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The Function of the Academy and Its Members During War and Peace

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WITH the entire nation engrossed in the all-important task of national defense, it is only fitting that each individual American seek out the job for which he is particularly suited and serve to the best of his ability. As pediatricians, it is up to us first to acquaint ourselves with our job and then to approach it in such a manner that it will be carried out with the maximum of precision and efficiency. The term national defense implies strengthening from within. A very famous Britisher once said, "Your great country will not be conquered by the vandals from without but will crumble as a result of disloyalty and treachery within." It is our contention that by starting at the very root of our social structure, our children, the next generation, and by strengthening the physical, mental, and moral fiber of that group, we shall build a firm foundation without which the rest of our program might well crumble.

If we remember that there are about thirty-six million children under 16 years of age in the United States and that about two million babies are born here annually and that in these small bodies and minds rests the national future, we can more readily appreciate the great concern of the nation regarding this group and visualize the scope of our own responsibility.

The history of World War I records great accomplishments by the medical profession and by certain of the specialist groups. The contributions of the pediatricians, however, not as individuals, comprise an unwritten chapter in that history. Future historians may be able to pass on to posterity a better record of achievement on the part of the pediatric group of this era.

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This was the opening paragraph of my address to Region IV at San Francisco in May, 1941. At that time I divided our task into three distinct periods: first, the period of National Emergency; second, the period of Actual Combat; and third, the period of Reconstruction. At that time I stated also to bear in mind that the responsibility does not end on our own shores but must be extended to foreign lands. Our program must be dedicated not only to the children of America, but also to the children of the world.

The aims of the pediatrist at this time are identical with those in time of peace—for every child, health protection from birth through adolescence; the building of a healthy next generation, sound in mind, in body and in purpose. Toward the achievement of this end, our work must proceed according to the basic fundamental principles laid down by the greater pediatric movements. We must consider, of course, the recommendations of the White House Conference on "Children in a Democracy" but with the added realization that new and unforeseen considerations are rapidly becoming apparent.

At this time we will consider only two stages: the period of Actual Combat and the period of Reconstruction.

First I should like to say that in this all-out war that all the members of the American Academy of Pediatrics are selected for this organization because they are trained to be good doctors in addition to being pediatricians. Every member of the Academy wishes to offer and has offered his services to his country as a physician. At the present time, 162 members of the Academy are now serving, and, in addition, there are many pediatricians who have not yet become eligible to the Academy who are now in the Army or Navy. At the present time, too, are many members of the Academy who saw active service in World War I. There are several who had extensive field service with the Red Cross. And of course there are many among us who by reason of age and physical handicaps are unable to serve in the field.

It seems to me that the Academy as an organization is now on trial. If it is ever going to be of great value, now is the time. There are 1,496 Academy members, with regional, state, and local organizations. Every part of this country is represented. Every member is selected for his training and ability in pediatrics by the National Board before becoming a member of this organization. Each individual community has its own problems. The problem met in Massachusetts is not the same as that of Arkansas. Each community has its organization which is most active in child health.

The plan of the Academy is to foster and to stimulate interest in pediatrics and to correlate all aspects of the work for the welfare of children which properly come within the scope of pediatrics. From this you will note the Academy wishes no credit but is interested only in the health, mental and physical, and the welfare of all the children.

When I began as Regional Director, the welfare projects of many states reported that such work was being done by various organizations and for that reason they could not see where the Academy was justified in a similar responsibility. My conviction is that the function of the Academy is to assist in child health whenever and wherever the necessity for such collaboration exists.

In the last presidential address, Dr. Smith outlined the national organization, showing the various committees and their functions. This national organization should govern and direct activities, but I believe that any substantial improvement in child health, both physically and mentally, should begin in the home. The proper procedure would be to train the mother. This could be best accomplished by the local organization by the members in the different communities. First train the family physician and through him the mother. A knowledge of nutrition, immunization, infection, mental training, and the various phases of child care could best be learned and carried out through this method.

The members of this organization have the knowledge which can be brought up to date every year by attending the general meeting. Our round tables and our symposiums and our personal contacts are of great importance and great benefit to the members, but this is not the true function of the Academy. There should be a great national educational campaign instituted, its method to depend on the conditions present in each locality. We should work with other organizations. We should gain the confidence of the general practitioners and the laity.

There are many organizations giving out information for personal gain, as radio talks on nutrition and the value of various cereals—I might go on indefinitely. These types of information while not outright misrepresentations border on such because they blatantly assert the true solution for what is a far more complicated problem.

In this present emergency each member of this Academy should take over the duties of those who are able to go into active service. The officers of the Academy should be considered as representatives of members and should instruct each member that he is equally responsible with the officer in initiation of a general program. The state and local groups should organize and develop an educational program.

Up to the present we have spoken more of the physical phase. Dr. Beverly in the June issue of THE JOURNAL OF PEDIATRICS, under the title "Reaction of Children and Youth to Wartime," gives us a splendid picture of the motions of the developing child during this period. Particularly do I wish to draw attention to the statement, "Youths can be made to feel not only that they are important in the country but that they are an important part of the country. American history in school paves the way for the development of love of country and the feeling that this is *my* country and that its future holds an important place in it for *me*." This is particularly applicable if we

wish to develop a generation of Americans who will weather the period immediately after the war and not fall into pitfalls like those we saw developing immediately after the last war.

Our professional predecessors were very fortunate in living through two generations with peace. Their lives and aspirations were conditioned by that pleasant fearless atmosphere. Those were the years when we did not even have an income tax.

While I was still in service in France, immediately after the last war, I read an article in an American magazine prophesying that there would be an even greater war with the same powers in 1940. Shortly after the last war Hitler began developing the German child, stressing a healthy body accompanied by a mind filled with hate. This child was developed purely for cannon fodder with one idea—that of a greater Germany. And the Japanese present even a blacker picture, for the Japanese child believes that if he dies for his country he goes directly to Heaven for his reward. Our children should be taught to love and live for their country.

I do not believe that the period directly after the war, even though we win, which we will and must, will be the millennium. Even in this country there will undoubtedly be inflation and a period of extravagant spending as that which followed World War I and disease comparable to the "flu" we had in 1918. The soldiers, many of them, will come home "war weary" and will preach the same doctrine as they did before. Although we are now all patriots, let us make this epidemic of patriotism endemic, not sporadic. Let us look the situation squarely in the face. We shall have many problems in America; our own as well as the children of the world will require our earnest endeavor. Let us organize now.

Up to the present this paper has been dealing largely with generalities. Now specific recommendations could be made. A program of this kind could be accomplished in three ways: first, by subsidization; second, by legislation; and third, by education. The first and second methods can be considered together.

The American public as a whole cannot be pauperized. The great "backbone" of America is the middle class. Any plan in which the mother and father can participate will be more successful than one outlined for them, even though they are given financial and other assistance. To accomplish results I am sure we all understand large spending is not necessary.

Subsidization can be accomplished by subscription and also by legislation. At times this form of assistance may be beneficial, but a great deal cannot be accomplished in this way.

There will be much legislation now and particularly in the period after the war, intended to benefit child health. Some of this legislation will be truly altruistic in purpose; other types will have selfish motives

behind them. Much of this legislation should be encouraged; some should definitely be defeated. The Academy through its legislative department can best direct such legislation so that the most benefit will result and, by working with national organizations and gaining their full confidence, can control and direct such legislation so that the most benefit would result.

Education is the most important method of promoting child health now and especially after the war. This can be accomplished by giving the right publicity through every possible means: publications, talks by members of medical and lay organizations, radio, film or movie, sound films. The Academy has at present the following publications:

The Journal of Pediatrics
Child Health Record
Report of Committee on Immunization and Therapeutics
Health Appraisal of the School-Aged Child
Film: "When Bobby Goes to School"

Now I wish to refer to the *Child Health Record*. Not only the medical profession but even Academy members are not sufficiently familiar with its purpose. The *Child Health Record* should be introduced into every home in America. If the mother were taught its true value, immunization and general care of the child would follow. Literally millions of American homes would save for other necessary purposes. Hundreds of millions of dollars can be spared; also much suffering and misery. We should introduce this Record into the various medical groups, and especially should the obstetrician be taught its value. Every mother when she comes to the obstetrician for care should be presented with the Record and should have its usage carefully explained. The "tree" demonstrates heredity and the value of prenatal care, as well as the care of the child. It may even be desirable to suggest to members of the profession that they should distribute these Health Records among their patients as part of an undertaking whose purpose is the best interest of the child. I urge the members of this Academy to introduce wherever possible the *Child Health Record*.

The present world crisis creates conditions which the medical profession must meet. New communities are springing up everywhere. Overcrowding and poor housing are typical, yet historically overcrowding and poor housing are the hatching centers of epidemics and of disease—tuberculosis is a case in point. These conditions require proper supervision of sanitation and nutrition, and particularly here, if we are faithful to our trust, we must mount guard to protect the child. Later we will face the greater problem of rehabilitation, with all of the difficulties that the term implies. Let me say that the pediatrician will prove his metal in the next decade.

Liaison of the Academy with other organizations might well be divided as follows:

I. Medical Profession
   (a) American Medical Association, representing the medical profession as a whole
   (b) National and local pediatric groups

II. Allied professions
   (a) Dentists and dental hygienists
   (b) Nurses
   (c) Physiotherapists
   (d) Technicians
   (e) Social workers

III. Lay Groups
   (a) Parent and others in the home
   (b) Teachers
   (c) Religious workers

IV. Institutions
   (a) Hospitals
   (b) Clinics
   (c) Schools, particularly medical colleges

V. Organizations especially interested in child welfare
   A. National
      (a) Children's Bureau
      (b) Parent-Teacher Associations
      (c) The American Legion
      (d) Junior League
      (e) Fraternal organizations
      (f) Scout movements
      (g) Y. M. C. A. and Y. W. C. A.
      (h) Religious groups
      (i) Service clubs
      (j) Insurance companies
      (k) Commercial laboratories
   B. Local
      (a) Private organizations
      (b) Local branches of national organizations
      (c) State and local Health Boards

I am giving in detail an outline of a number of the various organizations and their purpose for the reason that each will function best and be better organized in different communities; also each will have its purpose.

Among these agencies I mention first the American Medical Association and the medical profession. Only by enlisting the aid of the profession can we succeed in any ambitious program. Different conditions will be met in different states and communities. In some, organized medicine will work well with the Academy and in others there will be jealousy to overcome. This can be tactfully handled when the profession realizes as a whole that the Academy has no axe to grind but merely wishes to help.

The Children's Bureau now and always has worked together with the Academy and there should be close cooperation. I will quote from an active member of the Academy and a worker in both organizations. "No one, no matter how high up in officialdom, can speak with the authority of the pediatrician down among the grass roots where he is in daily contact with the child and with the child's environment."

As a national organization, I particularly wish to mention the Parent-Teacher Association and the Child Health Department of the American Legion. The Parent-Teacher Association is active in all communities in the United States and needs no further explanation here.

The Academy has been working with the Child Health Division of the American Legion for several years. The Legion has 1,130,000 members at the present time, and after this war the membership will be increased many times. This membership represents that many homes throughout the nation. Dr. Richdorf, Chief Liaison Officer to the American Legion, has done splendid work. Each state appointed a member of the Academy to work together with the Legion to institute a program. This was done and a list published in the roster of the Academy, but I fear with but few exceptions the men appointed have not been active. What can be done through the American Legion if we win their confidence has been demonstrated by Dr. Wylder and Dr. Adler in New Mexico.

The American Legion sponsers radio talks and movies, and particularly slide-sound method of education of the laity. Among its many other activities, the Legion is establishing day nursery facilities for children in war industry communities. The American Legion offers a program of sound films on the care and nutrition of the child. Its purpose is to instruct parents and others. This program is capable of reaching millions of homes with the proper cooperation between this Academy, its state organization, and the American Legion. The Academy without any financial responsibility may direct and control the Legion program. The Legion itself is quite willing to submit to us for our guidance the printed and visual aspects of this very desirable undertaking.

In conclusion I would say that the Legion program is an excellent method of reaching millions of homes to combat the problems of nutrition, immunization, contact infection, and sanitation, with which we have to deal every day.

Many states initiate their own programs. Especially do I want to mention what happened in Maryland. They have recently developed a scenario entitled "Child Health Conference" for group talks throughout the state for the personnel as well as the family.

Let me sum up the purpose of this presidential address; it is a plea to organize now and be ready to fulfill fully the functions for which the Academy was organized, to offer the services of pediatricians to our

country with no restrictions; to advise the best method of utilizing those of us who are not considered fit for service in the armed branches; to use the services of every man of the Academy both now and after the war; to remember that the function of the Academy is to achieve results and not to receive credit. I have not eulogized those organizations now working efficiently but purposely stressed new ones we might utilize.

My concept of what our Academy is and for what it stands follows: It is a working organization of physicians established for the purpose of helping the children of America and of the world. As an organization, it has accomplished a great deal, but its period of greatest value to civilization is still in the future. Criticism we must welcome. To a profession like ours it is the very breath of life. Let us remember that we share the fate of all other organized groups. We must go on. We must improve or we approach the state of the Pharisee of scriptural fame. I believe we were put in this world for a purpose; that we adopted pediatrics because we preferred that branch; that we succeed only as we help the child. I believe the American child should be reared to love and to protect this country, to grow up in peace and to have insured his future years such as we have had, and to be able to look forward to an era of hope rather than that period of uncertainties which culminated in the destruction of the second World War.

In closing, I can do no better than to quote the words of one of the wisest of all Americans, the late Mr. Justice Holmes: "I believe that the wholesale social regeneration which so many now seem to expect, if it can be helped by conscious co-ordinated human effort, can be affected appreciably only by taking in hand life and trying to build a race."

A NOTE ON THE PENETRATION OF POLIOMYELITIS VIRUS FROM THE GASTROINTESTINAL TRACT IN THE CHIMPANZEE*

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THE following experiment is cited as evidence that the abdominal sympathetic nerves may act as a pathway for the progression of poliomyelitis virus from the gastrointestinal tract of the chimpanzee. Numerous other observations have been described indicating that this animal is susceptible to inoculation of human strains of poliomyelitis virus by the oral or gastrointestinal route,[1] but in most instances it has not been possible to determine what pathways were utilized in reaching the central nervous system. In one case, previously recorded, there was strong evidence that the trigeminal nerve had served as the route of entry in an animal inoculated by mouth, but in the majority of the cases studied the animals were allowed to live until the development of extensive paralyses, at which time it was impossible to localize the precise point at which the virus entered the central nervous system.

The present note concerns a young male chimpanzee about 18 months old which was inoculated by stomach tube with human stool containing active poliomyelitis virus. Upon reception, the animal was suffering from an open osteomyelitis of the left maxilla. The cheek was much swollen, there was slight fever (102° F.; normal, about 101°), and the appetite was poor. Under chloroform anesthesia, the wound, which communicated with the mouth, was carefully cleaned with 10 per cent urea solution, and a tampon soaked with urea was put into the cavity. This treatment was repeated twice daily for three days, during which time the exudate disappeared from the wound, although a small piece of dead bone still protruded. The swelling of the cheek was completely reduced, while the temperature and appetite rapidly returned to normal. On the second day after reception and for two subsequent days, the animal received by stomach tube 20 c.c. of human stool which were known to produce paralysis and a marked febrile reaction upon intranasal inoculation into rhesus monkeys.

On the fourth day following the first inoculation the animal was found in a "delirious" state with a fever of 109° F. The extremities showed occasional spasms of clonic twitching, especially the arms. Muscular power was normal, but the deep reflexes were slightly diminished. The animal seemed to be hyperesthetic and responded to touch on any part

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of the body with vigorous cries. The back was slightly stiff. Cranial nerve musculature was normal, and the jaw wound looked clean and showed vigorously granulating surfaces. Lumbar puncture produced a clear fluid under slightly increased pressure, showing 8 lymphocytes per cubic millimeter and no globulin. Aerobic cultures of cardiac blood were sterile in blood broth and on blood agar.

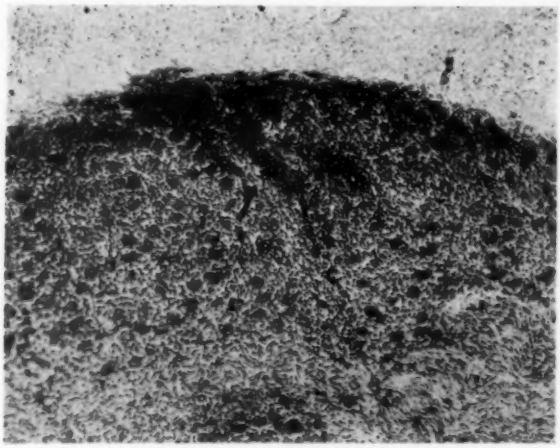

Fig. 1.—Celiac ganglion showing heavy infiltration of lymphocytes among the ganglion cells at the periphery and along an emergent bundle of nerve fibers (latter indicated by arrow). Gallocyanin stain ×100.

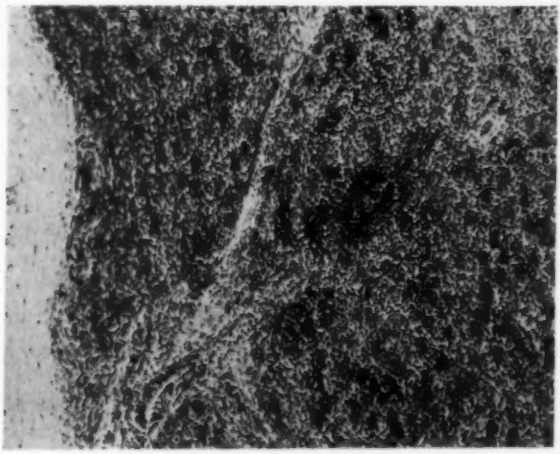

Fig. 2.—Celiac ganglion showing focal accumulation of lymphocytes in the gray matter adjacent to an emergent bundle of nerve fibers. Gallocyanin stain ×100.

The animal was killed, and pieces of liver and spleen were removed with sterile precautions. These were pooled, cultured both aerobically and anaerobically in blood broth and blood agar, and subsequently found to produce no signs of disease of the central nervous system upon intra-

cerebral inoculation into fifteen mice, ten guinea pigs, and three rabbits. The body was perfused with 1 per cent glacial acetic acid in 10 per cent formalin, and all the nervous centers, including the peripheral sensory and automatic ganglia, were removed. The osteomyelitic process was found to be localized to the alveolar process of the left maxilla. Although pus extended well into the left antrum, at no point did it approach the meninges. There was no suggestion of pneumonia or tuberculosis. The following tissues were sectioned serially at 10μ and stained with gallocyanin: ciliary, sphenopalatine, geniculate, submaxillary, Gasserian and celiac ganglia; sympathetic chains; cord levels C_3, C_8; T_4, T_7, T_{12}; L_4; dorsal root ganglia of C_2, C_3, C_4; T_5, T_6, T_7, T_8, T_9, T_{10}, T_{11}; L_1, L_3; S_2; olfactory bulbs; various levels of duodenum, jejunum, ileum, and colon. The medulla was cut serially at 60μ. All the tissues examined were normal except the coeliac ganglia and the right sympathetic chain. The latter showed some perivascular cuffing in the thoracic portion and a large area of lymphocytic infiltration in one of the lumbar ganglia. The celiac ganglia contained many areas of infiltration and cuffing which seemed to be localized in the gray matter immediately adjacent to the efferent nerves (Figs. 1 and 2). The lesions were identical with those observed in other chimpanzees inoculated by the gastrointestinal route.

DISCUSSION

The histologic evidence clearly indicates an inflammatory process confined to the abdominal portions of the sympathetic nervous system. Since the animal had received active poliomyelitis virus four days previously, it seems likely that these lesions were poliomyelitic, although no effort was made to demonstrate virus in the tissues at the same time. Furthermore, it is quite clear that the lesions and febrile reaction could not have been the result of the quiescent osteomyelitis. The failure to demonstrate either microorganisms or virus in the blood, liver, and spleen tends to rule out the few infectious agents which might produce a similar histologic picture, namely, equine encephalomyelitis, St. Louis encephalitis, and lymphocytic choriomeningitis, since in all these diseases the virus is found in the liver and spleen and is usually demonstrable by one of the types of rodent inoculation employed. Rabies could scarcely be considered as a possibility since it has not been found in human stools,[2] so that there seems to be reasonable assurance that the animal had preparalytic poliomyelitis. While it may be contended that the demonstration of the virus by animal inoculation would have been more accurate in establishing the disease in such an early case, this would be true only if virus were positively identified. We feel that, with proper control, the histologic method may often detect slight degrees of change in tissues where, for various reasons, virus cannot be demonstrated.

These findings suggest, then, that virus may invade the spinal cord from the gastrointestinal tract via the celiac ganglion and the sym-

pathetic chains. While reaction in these tissues is definite, nerve cell destruction is not great. The failure to find lesions in Auerbach's and Meissner's plexuses in the gut wall is probably of little significance considering the relatively small amount of tissue which could be examined, but it might be hazarded that in this site virus could be harbored without visible nerve cell damage.

The intestinal tract as a possible portal of entry in man is suggested by the finding of virus in the walls of the gut by various workers and in a human celiac ganglion by Sabin and Ward.[3] However, the presence of virus or lesions in these tissues in the terminal stages of paralytic poliomyelitis cannot be regarded as critical evidence with respect to the original portal of entry, since at such a time there has been overwhelming spread of virus. It has been observed, for example, that lesions were present in the celiac ganglia of a chimpanzee paralyzed following intranasal inoculation. Lesions in the celiac ganglia appear to be more readily correlated with the mere presence of virus in the feces of paralyzed animals than with the portal of inoculation.[1] Since it is virtually impossible to secure human pathologic material in the preparalytic stages, the only method for obtaining precise information on the invasion of the nervous system appears to be through the study of some of the higher primates, such as the chimpanzee, in which the actual pathway of the virus can be followed from mucous membranes to the central nervous system.

SUMMARY

Evidence is presented that in the chimpanzee poliomyelitis virus may reach the central nervous system from the gut via the abdominal sympathetic nerves.

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A STUDY OF PREMATURE MORTALITY

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IN 1935, the American Academy of Pediatrics, in the round table discussion on prematurity,[1] emphasized the need for increased and standardized studies on the mortality of premature infants. A range varying from 10 per cent or less in some hospitals in Chicago to 70 per cent in others has made it evident that a greater number of premature infants should be studied under some uniform classification. There was also expressed at the time of the Academy meeting a plea for a widespread study of this subject, dividing the premature infants into several weight groups, with particular emphasis on the mortality rates, length of life, and causes of death in the several groups.

The importance of this problem can once more be emphasized when it is noted that approximately one in ten live births is a premature infant. It was brought out in the Academy round table discussion on prematurity that Hadley, who made a study of 3,079 births in the New Haven Hospital, reported an incidence of 6 per cent prematurity; and Brandt reported 10.4 per cent prematurity in 5,439 live births in Cologne, Germany. Peckham,[2] in a study of all births at Johns Hopkins from 1896 to 1936, found that 4,055 were premature out of a total of 39,394 births. The importance of this problem can further be realized by the investigations into neonatal mortality, which reveal prematurity as a single cause accountable for 47 per cent of all neonatal deaths.[3]

Since 1937 there has been a decided lowering of the premature mortality in the Charity Hospital of Louisiana, at New Orleans, which is believed to be due to several definite factors. It is the purpose of this paper to present first a study of the premature mortality rate over the past four years in relation to the specific changes in environment and personnel in the nursery; and second, a detailed study of the causes of death in various weight groups in the 498 premature infants who died during this period.

MORTALITY RATES OVER THE PERIOD 1937-1940 INCLUSIVE

In 1937 there were 157 premature births in Charity Hospital. Of these, 134 died and 23 left the hospital alive. A survey of Table I will reveal the mortality rates for the various weight groups. The total mortality rate for the year was 85.3 per cent. During 1938 there were 159 deaths out of 216 prematures born alive, the total mortality rate

From the Department of Pediatrics, School of Medicine, Tulane University of Louisiana, and Charity Hospital.

TABLE I

MORTALITY RATES BY WEIGHT GROUPS FOR YEARS 1937-1940 INCLUSIVE

BIRTH WEIGHTS (GM.)	1937				1938				1939				1940			
	LIVING	DEAD	TOTAL	MORTALITY	LIVING	DEAD	TOTAL	MORTALITY	LIVING	DEAD	TOTAL	MORTALITY	LIVING	DEAD	TOTAL	MORTALITY
Under 1000	0	16	16	100%	0	22	22	100%	0	23	23	100%	0	23	23	100%
1001-1250	0	14	14	100%	0	28	28	100%	1	15	16	93.7%	3	17	20	85%
1251-1500	2	15	17	88.2%	3	11	14	78.5%	2	16	18	88.8%	5	12	17	70.6%
1501-2000	9	56	65	86.1%	21	61	82	74.4%	26	33	59	55.9%	72	38	110	34.6%
2001-2500*	12	21	33	63.6%	33	30	63	47.6%	55	27	82	32.9%	79	20	99	20.2%
Totals†	23	122	145	84.2	57	152	209	72.7	84	114	198	57.6	159	110	269	40.9
	23	*134*	*157*	*85.3*	*57*	*159*	*216*	*73.6*	*84*	*127*	*211*	*59.7*	*159*	*116*	*275*	*42.2*

*Average weight of this group = 2,166 Gm.

†Totals of cases, including those without birth weights.

for the year being 73.6 per cent (Table I). This year saw the beginning of segregation of premature infants from the general nursery infants. This was carried out, however, in the same nursery, premature infants being screened off in one corner of the room. Three residents were added to the pediatric staff during 1938.

In 1939 the total premature mortality rate decreased to 59.7 per cent, representing 127 deaths out of a total of 211 infants born alive (Table I). In this year graduate nurses were assigned to the care of the premature infants as a group. In addition, all premature infants weighing less than 3 pounds at birth were put on breast milk for varying lengths of time. Oxygen was used as a routine measure during the first twenty-four hours of life and as indicated thereafter. A closer cooperation between the obstetric and pediatric departments came into being at about this time, and all infants, including the premature ones who required resuscitation, were seen within the first few minutes of life by the resident pediatrician.

The mortality rate for the year 1940 was 42.2 per cent, a total of 116 deaths out of 275 live births (Table I). In January, 1940, the nursery was moved into the new building of Charity Hospital, where small adjoining rooms were set aside for the premature babies. These rooms were equipped with running water and a refrigerator. A small isolation room, which was used for both premature and older infants, was available. A graduate nurse, who had done postgraduate work on premature infants, was placed in charge of the nursing care of this section and additional nurses and personnel were added. Enough additional bassinets were obtained to insure an individual one for each infant.

THE MAIN CAUSES FOR THE 498 PREMATURE DEATHS

In reviewing the causes of death in the series of 498 premature deaths, various factors have been taken into consideration. Wherever a post-mortem examination was done, the pathologist's final diagnosis was considered the *final cause*. In some instances, nonetheless, the only diagnosis which could be arrived at following the post-mortem was *prematurity*. These cases have, therefore, been included in one group with those other cases in which a review of the clinical course and case record gave no clue to some nonanatomic diagnosis, such as *diarrhea*. This rather large group can thus be looked upon as death due truly to prematurity on that basis solely or death due to some unknown cause. As would be expected, most cases without autopsy fell under this heading.

The diagnosis of *atelectasis* was based solely on post-mortem findings. Where the autopsy revealed the atelectasis and some other additional pathologic condition, a consideration of the clinical record was used to determine the final diagnosis.

Bronchopneumonia was, in all cases, a post-mortem diagnosis.

TABLE II

A STUDY OF PREMATURE MORTALITY IN 859 CASES

MAIN CAUSES OF DEATH	PERCENTAGE	NUMBER
Atelectasis	24.22	121
Prematurity	22.08	110
Bronchopneumonia	15.07	75
Diarrhea	12.44	62
Cranial injury	11.05	55
Syphilis	4.61	23
All others	10.44	52
Total	99.91	498

TABLE III

A STUDY OF PREMATURE MORTALITY IN 859 CASES

CAUSES OF DEATH IN BABIES UNDER 1,000 GM. IN WEIGHT (16.9%)	PERCENTAGE	NUMBER
Atelectasis	41.6	35
Prematurity	38.1	32
Cranial injury	11.9	10
Syphilis	3.5	3
Bronchopneumonia	1.2	1
Adrenal apoplexy	1.2	1
Anencephalic monster	1.2	1
Total	99.7	83*

*Autopsies were performed on fifty-nine cases.

TABLE IV

A STUDY OF PREMATURE MORTALITY IN 859 CASES

CAUSES OF DEATH IN BABIES 1,000 TO 1,250 GM. IN WEIGHT (14.9%)	PERCENTAGE	NUMBER
Atelectasis	32.4	24
Prematurity	28.4	21
Cranial injury	18.9	14
Bronchopneumonia	8.1	6
Syphilis	4.0	3
Diarrhea	2.6	2
Hemorrhagic disease of newborn	1.3	1
Monster (agnathia and microstomia)	1.3	1
Upper respiratory infection	1.3	1
Aspiration pneumonia	1.3	1
Total	99.6	74*

*Autopsies were performed on sixty cases.

TABLE V

A STUDY OF PREMATURE MORTALITY IN 859 CASES

CAUSES OF DEATH IN BABIES 1,251 TO 1,500 GM. IN WEIGHT (10.9%)	PERCENTAGE	NUMBER
Atelectasis	38.9	21
Prematurity	22.2	12
Cranial injury	12.8	7
Bronchopneumonia	7.4	4
Syphilis	7.4	4
Diarrhea	7.4	4
Icterus gravis	1.8	1
Otitis media	1.8	1
Total	99.7	54*

*Autopsies were performed on thirty-five cases.

Diarrhea was separated from the respiratory infections, because it was felt that where there was an associated infection, this and not the diarrhea was the main cause of death. Thus, a case of upper respiratory infection with diarrhea was considered as a death due to the upper respiratory infection as the main cause.

Throughout this paper, the term *cranial injury* is used in a general sense to include all intracranial lesions, both injuries and hemorrhage. This diagnosis was made where post-mortem revealed the lesion. In those few cases in which two or more causes were found, a review of the clinical record was again the deciding factor in determining the final diagnosis.

All cases found at post-mortem to have pathologic evidence of *syphilis* were included in this group, regardless of other findings.

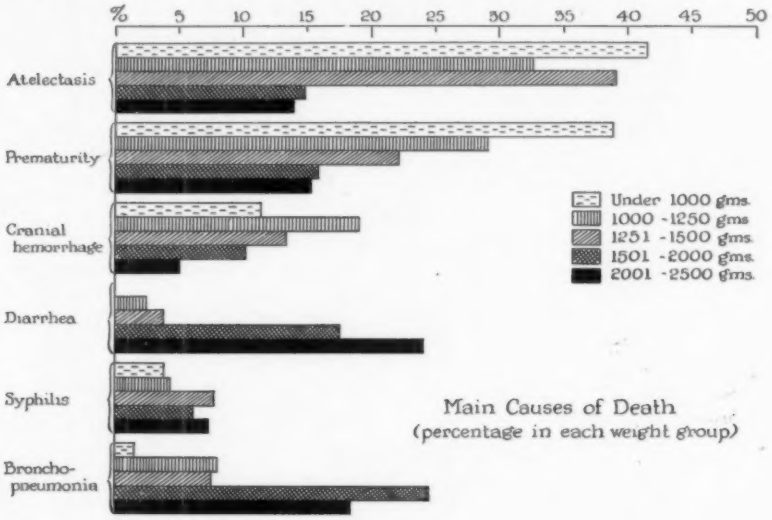

Chart 1.

A study of Tables I, II, III, IV, V, VI, and VII reveals a definite basis for the causes of death in premature infants. In our series of 498 deaths among premature infants (Table II), the most important single cause of death was atelectasis. Failure of the lungs to expand properly and to function was responsible for 24.2 per cent of all deaths. Atelectasis assumes double importance as a cause of death in all premature infants weighing less than 1,500 Gm. (Tables III, IV, and V and Chart 1.)

Prematurity alone was found to account for 22 per cent of the deaths in our series. Deaths due to unknown causes are also classified under this heading, but the majority in this group apparently died from prematurity alone; that is, their development had not progressed suffi-

TABLE VI

A STUDY OF PREMATURE MORTALITY IN 859 CASES

CAUSES OF DEATH IN BABIES 1,501 TO 2,000 GM. IN WEIGHT (37.6%)	PERCENTAGE	NUMBER
Bronchopneumonia	24.6	46
Diarrhea	17.6	33
Prematurity	15.9	30
Atelectasis	14.9	28
Cranial injury	10.1	19
Syphilis	3.2	6
Otitis media	2.1	4
Icterus gravis	1.6	3
Upper respiratory infection	1.6	3
Adrenal apoplexy	1.6	2
Abscess of lung	0.5	1
Gastrointestinal anomaly	0.5	1
Anencephalic monster	0.5	1
Pyonephrosis	0.5	1
Enlarged thymus	0.5	1
Otitis media, pneumonia, meningitis	0.5	1
Hydrocephalus	0.5	1
Septicemia	0.5	1
Peritonitis	0.5	1
Dermatitis exfoliata	0.5	1
Aspiration pneumonia	0.5	1
Total	98.2	188*

*Autopsies were performed on 126 cases.

TABLE VII

A STUDY OF PREMATURE MORTALITY IN 859 CASES

CAUSES OF DEATH IN BABIES 2,001 TO 2,500 GM. IN WEIGHT (19.7%)	PERCENTAGE	NUMBER
Diarrhea	24.4	23
Bronchopneumonia	18.4	18
Prematurity	15.3	15
Atelectasis	13.3	13
Syphilis	7.1	7
Cranial injury	5.1	5
Otitis media	4.1	4
Hemorrhagic disease of newborn	2.0	2
Upper respiratory infection	2.0	2
Abscess of lung	1.0	1
Cellulitis	1.0	1
Spina bifida	1.0	1
Cardiac hypertrophy	1.0	1
Adrenal apoplexy	1.0	1
Ulcerative enteritis	1.0	1
Pyodermia and pulmonary infaret	1.0	1
Aspiration asphyxia	1.0	1
Total	99.7	98*

*Autopsies were performed on sixty cases.

ciently to maintain life. Waddell, Purcell, and Wray,[4] as well as Grier and Lassky[5] use the term congenital weakness when referring to these infants.

Bronchopneumonia was responsible for 15 per cent of all deaths. Other acute respiratory infections and otitis media raise the total to 18.6 per cent. In our series, therefore, approximately one death in five was due to an upper respiratory infection. As a cause of death in

premature infants above the weight of 1,500 Gm., it leads all other factors (Tables VI and VII and Chart 1). This can be expected from one point of view; that is, infants above this weight usually lived a long enough period of time to become exposed to some infection (Chart 2).

Diarrhea was the fourth main cause of death, accounting for 12.4 per cent of all deaths. Again, in the larger weight groups, diarrhea assumed a place second only to bronchopneumonia. This group represents those cases of diarrhea associated with digestive disturbances or gastrointestinal infection rather than with some systemic infection.

The fact that the tissues of the premature infant, as a whole, are weak, renders the infant susceptible to injury from even minimal trauma. This is most particularly true of the cerebral tissues. *Cerebral injury* accounted for 11 per cent of all deaths. Interestingly enough, this cause of death occurred throughout all weight groups in almost the same relative numbers.

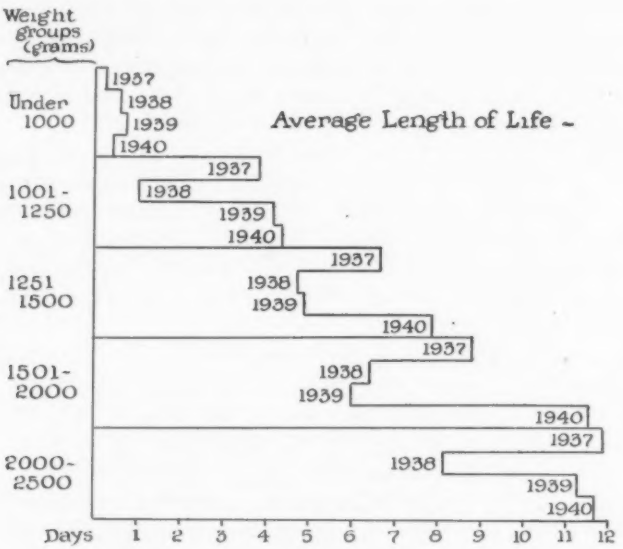

Chart 2.

Syphilis, the sixth main cause of death, represented 4.6 per cent of all deaths. Its occurrence in all weight groups was relatively the same.

The length of life of all premature infants who died was calculated for each weight group and is shown year by year in Chart 2. Premature infants of 1,000 Gm. or under lived an average of less than twenty-four hours. Those in the weight group of 1,000 to 1,250 Gm. lived four days on an average; those weighing 1,251 to 1,500 Gm. lived six days; those 1,501 to 2,000 Gm. lived eight days; and those weighing 2,001 to 2,500 Gm. lived ten and one-half days.

DISCUSSION

In presenting a four-year comparative study of mortality rates in premature infants, our main purpose has been an attempt to demonstrate how various factors have played an important role in decreasing the death rate from year to year. Singly, these factors appear almost insignificant, yet when considered in view of the marked decrease in premature mortality, they can be seen in their full import. We believe it appropriate here to emphasize the fact that since facilities for the premature infants at Charity Hospital have been and still are limited, it was necessary to admit to the premature nursery only those infants of 5 pounds in weight (2,268 Gm.) or less, except in the few cases where an infant weighing from 5 pounds to 5 pounds, 8 ounces, was found to be doing poorly. Only 36 of the total 859 infants came in this category. Over a four-year period, therefore, the average weight of our 2,000 to 2,500 Gm. group was only 2,166 Gm. We have emphasized this point because we believe an excellent standard of comparison of mortality rates by weight group subdivisions has been adopted, and we do not believe that the mortality for our largest group holds for the weight group of 2,000 to 2,500 Gm., but would more correctly hold for the weight group of 2,000 to 2,300 Gm.

We have not separated the mortality rates according to color because over the four-year period no significant statistical difference was found. It is to be noted, however, that the majority of the premature infants studied were colored, which could be expected because of the greater number of colored obstetric admissions and because of the well-established fact that the birth weights of the colored infants are generally lower.

The main causes for premature mortality are in order of frequency in our series: (1) atelectasis, (2) prematurity, (3) bronchopneumonia, (4) diarrhea, (5) cranial injuries, and (6) syphilis.

The striking thing about an appraisal of these causes is that for the most part these are *preventable deaths!* Atelectasis has long been the nemesis of the pediatrician and the obstetrician alike. An understanding of the methods of resuscitation of the newborn infant with a definite plan[6] involving the maintenance of warmth, immediate clearing of airways, gentle handling of the infant, and appropriate and judicious use of stimulants, remains a primary consideration. The use of the various resuscitators and the routine use of oxygen during the first forty-eight hours, with the interval use of carbon dioxide and oxygen mixtures through these critical hours are also of paramount importance.

If prematurity were the only cause of death in premature infants, we would feel that we had reached the acme of perfection in their care. It is true that some premature babies are simply too small or too weak to live. On the other hand, we believe that with further knowledge

and working out of routine techniques for the care and feeding of these infants, their mortality can be decreased. Incubators are of great importance in the very small premature infant, but a word of caution may be interjected here. Unless the use of the incubator is fully understood and unless there is an adequate nursing staff, the incubator, by its tendency to overheat the infant, may be actually detrimental.

The use of proper gowns and masks and the strict adherence to the aseptic technique are important in the prevention of infections. A face mask, however, may give one a false sense of security. All persons with any degree of upper respiratory infection should be excluded entirely from the nursery.

The ideal premature nursery would be an entirely separate unit, with an additional separate room for the isolation of all infected infants. The cubicle unit containing three or four bassinets, with one nurse taking care of only one cubicle, would appear to answer the problem of infection most adequately.

Many cases of diarrhea are due to an associated upper respiratory infection, the so-called reflex or parenteral diarrhea. A consideration of those other cases becomes mainly a discussion of the dietary regime of prematures. It is well known that the feeding of the premature is no simple problem, and in the absence of an adequate supply of breast milk, it becomes a very complex one. Weak tea in place of water, and the addition of a small amount of skimmed lactic acid milk to the twenty-four-hour formula, has been used in our series as a prophylactic measure against diarrhea. Because of the lack of adequate amounts of breast milk, we have been forced to use powdered milk formulas as a substitute, with a fair degree of success.

Trauma resulting from passage through the birth canal is likely to cause some degree of cranial injury in almost all premature infants, due to the fact that their tissues are weaker and their skull bones are softer.[7] The prophylactic and therapeutic use of vitamin K in cases of cranial injury would seem to offer a promising effective agent.

The reduction of syphilis as a cause of deaths among premature babies resolves itself into the public problem of reducing syphilis in the population generally and specifically among prepartal mothers.

SUMMARY

The study of premature mortality remains an important one. In 1938, 31,100 neonatal deaths were reported by the United States Bureau of the Census as directly due to premature birth.

We have presented the following:

1. A comparative mortality study among the 859 premature births at the Charity Hospital of Louisiana, in New Orleans, over the years 1937-1940 inclusive.

2. The main causes of the 498 deaths occurring in the series studied, using the standard weight groups adopted by the American Academy of Pediatrics for tabulation.

3. The average term of life in each weight group of the premature infants who died.

4. Our observation of the factors responsible for the decrease in mortality at Charity Hospital and suggestions therefrom for the continued and further lowering of the mortality rate.

Acknowledgment is made of the technical and literary assistance of Miss Ottilie M. Lambert.

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ENZYMIC THERAPY IN INFANT FEEDING

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AS THE activity of trypsin and amylase is decreased in the duodenal contents of infants suffering from digestive disturbances,[1, 2, 3] it is at least plausible to suppose that five factors may be responsible for the production of diarrhea in infants: (1) a primary cause which may be different in individual cases, namely, external heat, fever, infections, overfeeding, or an improper diet; (2) a reduction in the activity of the duodenal enzymes and secretions as a result of the primary insult; (3) an accumulation of undigested and unabsorbed food in the duodenum as a consequence of the reduction in enzymic activity; (4) the invasion of this undigested and unabsorbed food in the small intestine, which normally is relatively empty and sterile, by the fecal organisms from the cecum and large intestine; and (5) the fermentation of this food by these organisms and the formation of irritating end-products which accelerate peristalsis and produce diarrhea.[1]

The fourth and fifth factors in this sequence, as well any infection, can be adequately controlled by sulfathiazole and sulfaguanidine therapy,[4] or preferably it can be prevented by the use of 0.75 per cent lactic acid in milk fed to infants.[5] This paper reports an attempt to repair the second factor of reduced duodenal enzymic activity by the oral administration of commercial enzymic preparations to twenty-three infants.

In adults, it has been reported that a large part of the activity of enzymic preparations administered orally is destroyed in the stomach, and it has been claimed that they cannot significantly augment the digestive processes in the duodenum.[6] However, experiments on depancreatized dogs as well as on patients with achylia pancreatica indicate that pancreatic and other enzymic products given orally are not inactivated by gastric juice and increase the digestion of protein, fat, and carbohydrate.[7] Furthermore, infants fed milk, to which pancreatic proteolytic enzyme has been added to soften the curd, develop normally and have less diarrhea and infection of the upper respiratory tract than those in a like environmental situation on control milks.[8]

The dose of enzymes to be given the patients in this study was determined by calculating the amounts of amylase and trypsin secreted in the duodenal contents of infants with apparently normal digestion. The mean normal amylase and trypsin values per cubic centimeter are

From the Departments of Pediatrics of the Johns Hopkins and Duke Universities. Dr. Laslo Kajdi, as an impartial observer, analyzed the histories of the patients in this series to determine the effect of enzymic therapy. His assistance is gratefully acknowledged.

671 and 122 units, respectively, and the mean duodenal secretion per hour is 7.7 c.c.,[3] or 184.8 c.c. in twenty-four hours. In other words, a normal infant produces at least 124,000 amylase units and 22,545 trypsin units daily. The actual amounts probably are larger as an additional quantity is lost down the jejunum and is not collected by the duodenal tube. As may be seen in Table I, 0.3 Gm. pancreatin (A), 3.2 Gm. desiccated pancreas, and 41 Gm. holadin will supply these amounts of trypsin with an excess of amylase.

TABLE I

THE AMYLASE AND TRYPSIN ACTIVITY OF THE ENZYMIC PREPARATIONS FED TO THE PATIENTS (MEAN VALUES OF SEVERAL VISCOMETRIC TITRATIONS)[9, 10]

PREPARATION	AMYLASE UNITS PER GM.[10]	TRYPSIN UNITS PER GM.[9]
Pancreatin (A) (Extract of the entire pancreas*)	350,000	72,000
Desiccated Pancreas (Dried and powdered pancreas*)	500,000	7,000
Pancreatin (B) (Extract of the entire pancreas†)	31,350	?
Holadin (Extract of the entire pancreas†)	37,500	550
Taka-Diastase (Powdered extract of Aspergillus oryzae‡)	7,500	?

*The Armour Laboratories.
†Fairchild Bros. & Foster.
‡Parke-Davis Co.

Twenty-three infants suffering from digestive disturbances were given commercial enzymic preparations in total daily amounts which contained 85,500 to 10,500,000 amylase units and 990 to 2,160,000 trypsin units. Twenty-two of them were fed these products six to eight times daily for from three to eighteen days (Table II), and one patient received only one dose (Table IV). All of the infants took these preparations without difficulty. Eighteen had acute diarrhea of varying severity, four had chronic diarrhea (sprue, celiac diseases),[11] and one had pyloric stenosis. Their ages varied from 5 to 36 months, and their weights, from 3,210 Gm. (7 pounds, 2 ounces) to 10,620 Gm. (23 pounds, 9 ounces) when the oral administration of the enzymic preparations was started.

Sixteen of the twenty-three infants were apparently benefited; their daily weight gains varied from 15 Gm. (½ ounce) to 112 Gm. (3¾ ounces), with a mean of 37 Gm. (1¼ ounces), their appetites usually improved, and their stools generally became formed and fewer in number. In seven of the patients no clinical effect, good or bad, could be noted; four of them had severe infections (otitis media, pneumonia, or pyuria), one had only one dose (Table IV), and one record was lost. However, the fact that the extent of the weight gain was not

TABLE II

ORAL ADMINISTRATION OF ENZYMIC PREPARATIONS TO TWENTY-THREE INFANTS SUFFERING FROM DIGESTIVE DISTURBANCES[a]

CASE NO.[a]	AGE (MONTHS)	WEIGHT BEFORE ENZYMIC THERAPY (GM.)	ENZYMIC THERAPY			
			DAILY AMYLASE (UNITS)[10]	DAILY TRYPSIN (UNITS)[9]	DURATION (DAYS)	AVERAGE DAILY WEIGHT GAIN DURING THERAPY (GM.)
1	5	5,010	85,500[d]	990	4	75
2	14	5,790	85,500[d]	990	4	90
3	9	6,750	85,500[d]	990	5	24
4	13	7,320	85,500[d]	990	12	15
5	23	8,910	85,500[d]	990	5	108
6	7	5,400	85,500[d]	990	8	−7 (Loss)
7	7	3,480	85,500[d]	990	4	−82 (Loss)[b]
8	6	4,110	85,500[d]	990	7	−17 (Loss)[b]
9	9	3,300	150,000[e]	220	8	0[b]
10	5	4,230	150,000[e]	220	15	?
11	5	8,100	168,750[f]	2,475	3	0[b]
12	10	5,370	168,750–337,500[g]	2,475–4,950	15	18
13	30	8,490	168,750–337,500[g]	2,475–4,950	15	32
14	6	5,070	940,500[h]	+	6	48
15	14	5,940	940,500–10,500,000[i]	2,160,000	5	42[c]
16	36	10,620	940,500–10,500,000[j]	2,160,000	18	25
17	14	7,800	5,250,000[k]	1,080,000	12	50
18	27	7,650	5,250,000[k]	1,080,000	4	112
19	11	7,350	5,250,000–7,500,000[l]	105,000–1,080,000	16	13
20	14	7,830	5,250,000–7,500,000[l]	105,000–1,080,000	16	19[c]
21	8	5,790	7,500,000[m]	105,000	6	30
22	6	3,210	7,500,000[m]	105,000	6	15
23						

(See Table IV)

[a]The patients in cases 1 to 12, 14, 15, 19, 20, 21, and 23 had acute diarrhea, those in cases 13, 16, 17, and 18 had chronic diarrhea (sprue, celiac disease),[11] and the one in case 22 had pyloric stenosis.

[b]The patients in cases 7, 8, 9, and 11 had severe infections (otitis media, pneumonia, or pyuria).

[c]The patients in cases 15 and 20 were given blood transfusions.

[d]0.3 Gm. holadin (the contents of two capsules) and 0.4 Gm. taka-diastase, (the contents of two capsules) were given in each feeding (6).

[e]15 c.c. (½ oz.) of a 3.3 per cent suspension of holadin in tap water (0.5 Gm. holadin) and 16 mg. (¼ gr.) saccharin were given by nursing bottle after each feeding (8).

[f]22.5 c.c. (¾ oz.) of a 3.3 per cent suspension of holadin in tap water (0.75 Gm. holadin) and 16 mg. (¼ gr.) saccharin were given by nursing bottle after each feeding (6).

[g]22.5 c.c. (¾ oz.) of a 3.3 per cent suspension of holadin in tap water (0.75 Gm. holadin) and 16 mg. (¼ gr.) saccharin were given by nursing bottle after each feeding (6) for the first eight days; for the next seven days the strength of the holadin suspension was doubled.

[h]15 c.c. (½ oz.) of a 33.3 per cent suspension of pancreatin (B) in tap water (5 Gm. pancreatin) were given by nursing bottle after each feeding (6).

[i]15 c.c. (½ oz.) of a 33.3 per cent suspension of pancreatin (A) in tap water (5 Gm. pancreatin) were given by nursing bottle after each feeding (6) for the first three days; for the next two days pancreatin (B) was substituted for pancreatin (A).

[j]15 c.c. (½ oz.) of a 33.3 per cent suspension of pancreatin (A) in tap water (5 Gm. pancreatin) were given by nursing bottle after each feeding (6) for the first fourteen days; for the next four days pancreatin (B) was substituted for pancreatin (A).

[k]30 c.c. (1 oz.) of an 8.3 per cent suspension of pancreatin (A) in tap water (2.5 Gm. pancreatin) were given by nursing bottle after each feeding (6).

[l]30 c.c. (1 oz.) of an 8.3 per cent suspension of pancreatin (A) in tap water (2.5 Gm. pancreatin) were given by nursing bottle after each feeding (6) for the first five days; for the next eleven days desiccated pancreas was substituted for the pancreatin.

[m]30 c.c. (1 oz.) of an 8.3 per cent suspension of desiccated pancreas in tap water (2.5 Gm. desiccated pancreas) were given by nursing bottle after each feeding (6).

related to the dose of enzymic units administered or to the product employed may indicate that: (a) the enzymic therapy had nothing to do with the patients' improvement, or (b) the amounts of enzyme given were above the minimal requirements. In other words, the oral administration of commercial enzymic preparations is harmless and possibly is beneficial.

TABLE III

THE AMYLASE AND TRYPSIN ACTIVITY OF THE DUODENAL CONTENTS OF THREE PATIENTS WITH DIARRHEA AND FOUR WITH SPRUE BEFORE THE ENZYMIC THERAPY WAS STARTED; AVERAGE VALUES OF SEVERAL VISCOMETRIC TITRATIONS[9, 10]

DIAGNOSIS (AND PATIENT)	AGE (MONTHS)	AMYLASE UNITS PER C.C.[10]	TRYPSIN UNITS PER C.C.[9]	DUODENAL SECRETION IN C.C. PER HOUR*
Diarrhea (Case 10)	5	10	32	17.6
Diarrhea (Case 14)	6	283	104	11.8
Diarrhea (Case 23)	?	674	(Not titrated) 47	7.0
Sprue (Case 13)	30	237		14.5
Sprue (Case 16)	36	5,377	33	14.9
Sprue (Case 17)	14	738	18	14.0
Sprue (Case 18)	27	873	49	10.2
Mean	20	674	40	14.0
(Mean normal)[3]		(671)	(122)	(7.7)

*These amounts represent only the duodenal contents collected by siphonage for three to six hours. An additional quantity probably was lost down the jejunum. Accurate measurements can be obtained by the use of a Miller-Abbott tube with inflated balloons above and below the duodenal bucket.[12]

The strength of the duodenal amylase and trypsin of seven of the twenty-three infants was titrated before the oral administration of the enzymic preparations was started (Table III). the amylase content was normal, but the trypsin activity was markedly reduced. The duodenal secretion per hour was double that of normal,[3] but as previously stated, these quantities are inaccurate. No explanation could be found for the high amylase value in the patient in Case 16, as it usually is not increased in chronic diarrhea (sprue, celiac disease).[1, 2] Comparison with previous titrations of the duodenal contents of normal infants[1] cannot be made because different lots of starch and gelatin were used as substrates.[13] As the other sixteen infants in this series were suffering from similar digestive disturbances, they probably had comparable duodenal enzymic values.

Only one duodenal titration was made after the enzymic feeding, and that was done immediately after the first dose (Table IV). The fact that the average amylase units in this patient rose from 674 per cubic centimeter before pancreatin was given to 3,417 for the two hours

following its administration indicates that the enzymic activity of pancreatin is not destroyed by the gastric juice.[7] During the next hour, however, the amylase content fell to its previous level, and the excess due to pancreatin had disappeared.

TABLE IV

THE EFFECT OF FEEDING PANCREATIN ON THE AMYLASE ACTIVITY OF THE DUODENAL CONTENTS OF A PATIENT WITH DIARRHEA (CASE 23); AVERAGE VALUES OF SEVERAL VISCOMETRIC TITRATIONS[9, 10]

	DUODENAL CONTENTS		
TIME	AMOUNT* (C.C.)	pH	AMYLASE UNITS PER C.C.†
11:10 A.M.-12:00 N.	3.8	7.6	880.5
12:00-1:30 P.M.	10.0	7.6	959.0
1:30-2:35 P.M.	8.8	7.6	582.5
2:35-2:50 P.M.	3.0	7.9	269.5
Average	7.0 per hr.	7.6	674.0
2:50 P.M.	44 c.c. 10% pancreatin (A) was fed by nursing bottle (4.4 Gm. pancreatin (A); pH 5.8; 1,540,000 amylase units; 316,800 trypsin units (Table I).		
2:50-3:05 P.M.	13.7	5.9	3,140.0‡
3:05-4:25 P.M.	5.5	5.4	3,695.0
Average	12.1 per hr.	5.6	3,417.0
4:25-5:45 P.M.	9.0	5.4	329.0

*See footnote (*) to Table III.

†Two per cent starch at pH 7.0 was used as a substrate.[10]

‡This specimen contained a considerable amount of pancreatin which had been fed to the infant fifteen minutes previously.

SUMMARY

Commercial enzymic preparations, which contained 7,500 to 350,000 amylase units and 550 to 72,000 trypsin units per gram, were administered orally to twenty-three infants suffering from digestive disturbances in doses of 0.3 to 1.5 Gm. holadin, 0.4 Gm. taka-diastase, 2.5 to 5.0 Gm. pancreatin, or 2.5 Gm. desiccated pancreas six to eight times daily for from three to eighteen days, except for one infant who received only one dose. Sixteen of the patients were apparently benefited with gain in weight, improvement in appetite, and reduction in the number of stools. No clinical benefit or harm could be noted in the other seven, four of whom had severe infections in addition to diarrhea. The amylase activity of pancreatin is not destroyed by gastric juice.

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THE TREATMENT OF ICHTHYOSIS WITH VITAMIN A

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MANY remedies[1] have been recommended for ichthyosis by various authors. External application of greases is frequently prescribed as a palliative. However, no internal remedy is widely accepted, and only thyroid medication has a number of adherents.

Some advocates of thyroid extract have postulated a thyroid deficiency as the basis of ichthyosis. However, the characteristic cutaneous manifestation of hypothyroidism is myxedema. Some dryness and scaliness of the skin, when present in the latter, might be attributed to deficiency of vitamin A, caused by failure of conversion of carotene to vitamin A in the absence of thyroid hormone.[2] Mumford[3] reported that the benefit from thyroid medication in ichthyosis is greater in the presence of evidence of thyroid deficiency. Porter,[4] also an advocate of thyroid therapy, found a low basal metabolism in seven out of ten children and in two out of eight adults with ichthyosis. At the same time, however, he stated that the degree of ichthyosis present is no guide to the basal metabolic rate in that patient, and that the most severe cases may have a normal or hypernormal basal metabolic rate. Tests were performed upon two of our six patients reported in this paper. One boy had a rate slightly below average but probably within normal limits (–4, –13, and –8 per cent at various times). A woman, aged 35 years, gave a history that her basal metabolic rate had been –20 to –30 per cent, and that she had taken 2½ gr. of thyroid extract daily for years but without any cutaneous improvement. Our other patients were not tested, but they exhibited no clinical symptoms of hypothyroidism. Talbot and Hendry[5] discovered no instance of a subnormal basal metabolic rate among eight ichthyotic children. Therefore, the latter authors concluded that ichthyosis in the majority of cases is not due or related to hypothyroidism and that the benefit derived from thyroid extract is not sufficiently marked to warrant a continuance of the treatment with any great amount of enthusiasm. Similarly, Bruhns[6] has reviewed all available literature in his authoritative monograph and states that a hypofunction of the thyroid gland has not been established in ichthyosis.

Cod-liver oil has been used empirically for many years in the treatment of ichthyosis. Brocq,[7] for example, advocated cod-liver oil (and

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Dr. Michael S. Shea, New Haven, Conn., kindly permitted us to use his observations of the effect of vitamin A upon himself.

Dr. Henry Friedman, Miss Belle Herman, R.N., and Miss Mary Gray, R.N., of the New York Association for Jewish Children, gave valuable cooperation in this study.

The vitamin A used in this investigation was supplied by the Abbott Laboratories, North Chicago, Ill.

arsenic) internally in doses as large as the patient would tolerate, given over prolonged periods. Vogel[8] noted a clinical and biophotometric improvement in several patients with ichthyosis treated with vitamin A. Vail,[9] reported a 9-year-old boy with corneal nodules and congenital ichthyosis and credited to vitamin D the improvement in the ocular and cutaneous lesions that followed large doses of both vitamin A and D. Wise and Sulzberger[10] stated, "Some patients with mild ichthyosis as well as other hyperkeratotic, parakeratotic, and dyskeratotic conditions are benefited, at least to some degree and for some time, by administration of high doses (10,000 to 300,000 units) of vitamin A for several months." Wise and Sulzberger felt that this result does not in any way contradict the established nevoid hereditary character of many of these conditions and that it does not necessarily indicate that ichthyosis, keratoses, and dyskeratoses of various kinds are true vitamin A deficiencies. Previously, however, because of the therapeutic response of such conditions to vitamin A, Wise and Sulzberger[11] had expressed the belief "that many patients without obvious dietary deficiency of vitamin A and without night blindness or other manifestations of vitamin A deficiency may nevertheless be suffering from mild degrees of local, relative hypovitaminosis A of the skin."

Observers[12] in various countries during recent years have described cutaneous manifestations of vitamin A deficiency, particularly a disorder sometimes termed phrynoderma. This dermatosis is characterized by keratotic plugs protruding from hair follicles, especially on the extensor surfaces of the extremities, and, in our opinion, is identical with keratosis pilaris or follicular ichthyosis. Our[13] previously reported experience with vitamin A therapy in this condition posed the question to us of the possible value of vitamin A in ichthyosis vulgaris (vera, simplex).

CONSIDERATIONS LINKING ICHTHYOSIS TO VITAMIN A DEFICIENCY

The frequent association in the same patient of both ichthyosis and the generally accepted cutaneous manifestations of avitaminosis A hints of some relationship. Practically all textbooks[14] describe follicular horny plugs containing coiled unerupted hairs, designated keratosis pilaris, as often present in cases of ichthyosis vulgaris along with typical desquamating, polygonal scales. The keratosis pilaris in these patients is usually indistinguishable from similar lesions ascribed by various authors[12, 13] to vitamin A deficiency. Conversely, illustrations of phrynoderma, recorded by Rao[15] show dry ichthyotic skin on the patients' legs. This combination has been observed by us as well. Furthermore, Rao[16] published photographs of a man aged 20 years with severe vitamin A deficiency, resulting in loss of vision due to keratomalacia, whose skin closely resembled ichthyosis and was labelled by R. E. Wright, "giraffe skin." The simultaneous occurrence in individuals of combinations of the various lesions mentioned above suggests a common etiologic factor.

Clinical similarities also intimate a relation between phrynoderma, the already established cutaneous manifestation of vitamin A deficiency, and ichthyosis. In both conditions, for example, there is almost always a seasonal fluctuation with great amelioration or complete return to normalcy during the summer. Factors in this cyclic variation might be the higher vitamin A content of the diet[17] during the summer months and the disturbance in vitamin A utilization resulting from the greater incidence of infections during the winter season. The frequent delay in the first appearance of ichthyosis until after weaning[4] (except harlequin fetus) suggests a dietary factor. Clinically, in both phrynoderma and ichthyosis there is a marked dryness of the skin with deficient or absent sweat and sebaceous secretions. Also in both conditions there is a predilection for involvement of the same regions, particularly the extensor surfaces of the extremities with a sparing of the flexor folds.

Pathologic similarities also favor the assumption of a relation between phrynoderma and ichthyosis. In both disorders there is a hyperkeratinization with excessive proliferation and cornification of the horny layer of skin. This process in phrynoderma involves particularly the hair follicles, whereas in ichthyosis there is greater involvement of the skin between the follicles.

PLAN AND SCOPE OF STUDY

The foregoing clinical and pathologic considerations suggested to us that vitamin A deficiency might be a factor in ichthyosis. We, therefore, determined to investigate our patients with this disorder for vitamin A deficiency and, if present, to observe the effect of intensive vitamin A therapy. The following investigation deals with a series of six patients, two adults and four children, all presenting the clinical syndrome of congenital ichthyosis. These patients have all received large amounts of vitamin A either enterally or parenterally, and the clinical results therefrom have been noted, and, in most of the cases, checked by means of the biophotometer.

PHOTOMETRIC INVESTIGATIONS

We have tested our patients with ichthyosis for vitamin A deficiency with the biophotometer. Criticisms of this instrument have been effectively answered by the recent paper of Jeans, Blanchard, and Satterthwaite,[18] who reaffirm its validity in detecting impaired dark adaptation. They have furthermore been corroborated by Eckardt and Johnson,[19] who obtained comparable results with the adaptometer and the biophotometer.

We were able to test five of our patients and they all yielded preliminary tests in the deficient zone. After intensive therapy the tests of all were within normal limits. Expressed in millifoot candles of light, normal for the biophotometer is below .07; borderline is from 0.7 to 1.0; deficient is above 1.0 after exposure to bright light. One boy gave a

just normal (0.69 preliminary test in mid-July when his skin was seasonally improved, but treatment was withheld and a subsequent preliminary test in mid-October when his skin was much worse showed deficiency (1.24). Treatment of five months' duration, consisting of thirty-five intramuscular injections, each of 100,000 international units of vitamin A, resulted in a gradual but great improvement of the skin, beginning at the end of the first month and reaching the maximum at the end of this course of therapy. As this child was treated out of town, a retest of the eyes was not feasible until the end of the fifth month, when there was a normal biophotometric test (0.35). Another boy was followed with frequent photometric studies for a period of approximately one year. Four preliminary examinations were all in the deficient zone (1.6, 1.4, 1.9, 1.3). Immediately after the fourth examination he was given what we have termed a "therapeutic test for immediate retinal response," consisting of the oral administration of 200,000 international units of vitamin A. One hour later the biophotometer test showed normal dark adaptation (0.35); two hours later it was already past the peak of the response (0.84); and at the end of twenty-four hours the test was back at the preliminary level (1.4). With a daily oral dose of 200,000 international units of vitamin A, there was not only a great improvement of the skin, but the biophotometric test was maintained at a better level (1.0 or less). However, we were unable to relieve permanently and completely the vitamin A deficiency in this case, for in spite of continuous oral therapy, which effectively sustained the skin improvement, there was a relapse in the biophotometric tests during the following winter. Bile salts to promote absorption of vitamin A were also administered during this period, when visual tests were in the deficient zone, but were ineffective in improving the visual dysadaptation. Seasonal fluctuations in the response to photometric tests have been reported by Pett[20] and by Jeans, Blanchard, and Satterthwaite,[18] and the seasonal factor is discussed by us in a later section of this report. The partial relapse, involving only the retina in this case while under vitamin A treatment, was confirmed by a number of tests. It was definitely a seasonal effect superimposed upon the resistance to vitamin A therapy, which has been observed in individuals deficient in vitamin A. For example, Getz, Hildebrand, and Finn[21] found that large doses of vitamin A may be required in such individuals to restore a normal response to photometric tests for impaired dark adaptation. Similarly, Hecht and Mandelbaum[22] found that in some individuals with an experimentally produced deficiency in vitamin A a return of visual tests to normal occurred only after vitamin A was administered for prolonged periods of time. That the relapse of our patient involved only the retina is not surprising, as frequently this is the first and only symptom of mild vitamin A deficiency.

Both the dark dysadaptation before therapy in all five patients tested and the visual improvement after treatment raise the question of the

relation between vitamin A deficiency and ichthyosis. Our series of cases is concededly small, but our investigations with the biophotometer definitely support the assumption that a disturbance in vitamin A metabolism may be an important etiologic factor in ichthyosis.

TECHNIQUE AND RESULTS OF VITAMIN A THERAPY IN ICHTHYOSIS

Because of the finding of impaired dark adaptation in our cases of ichthyosis and because of the similarities between accepted skin manifestation of vitamin A deficiency and ichthyosis, we decided to submit our patients to a therapeutic test for skin improvement with vitamin A. It seemed that a cure was possible because the marked spontaneous betterment of all but one of our patients during warm weather demonstrated the reversibility of the cutaneous pathologic process. Due to our previous experience[13] with phrynoderma, relatively large doses of vitamin A administered over prolonged periods were deemed necessary. In one patient administration by the oral route alone was employed, in three others the intramuscular route was used exclusively, while in two both routes were tried at different periods. Orally, a daily dose of 60,000 to 200,000 international units of vitamin A in the form of A-D percomorph oil was given for several months. Intramuscularly, "vitamin A, injectable," containing 100,000 international units of vitamin A and practically no vitamin D in 1 c.c. of vegetable oil, was administered two to three times a week for several months. The use of the latter preparation excludes the possibility that vitamin D might have been a factor in the effects obtained.

Our results with the above vitamin A therapy were in every instance favorable, and all patients obtained an amelioration which they deemed worth while. This is in accord with reports of Wise and Sulzberger[10] and Vogel.[8] In none of our patients was a perfectly normal skin secured. However, the patients' condition in March was as good as it usually was in July, so that a marked betterment compared with previous winters resulted. Although the skin was thickened at the beginning, after several months of vitamin A therapy, it was of more normal texture. Cracks and fissures, previously produced by scratching in the more indurated portions of the skin, disappeared entirely. The pruritus also was considerably diminished. The scales became thin, superficial, and more widely separated. There was increased activity of the sweat and sebaceous glands so that the surface, previously dry and rough, appeared glossy and felt smoother and more oily. Almost all areas of the skin were definitely better and some parts became completely normal. Improvement was generally discernible at the end of a month of vitamin A therapy and was progressive for several months while the treatment was continued, but whenever the vitamin A was stopped for an appreciable time, the skin became worse.

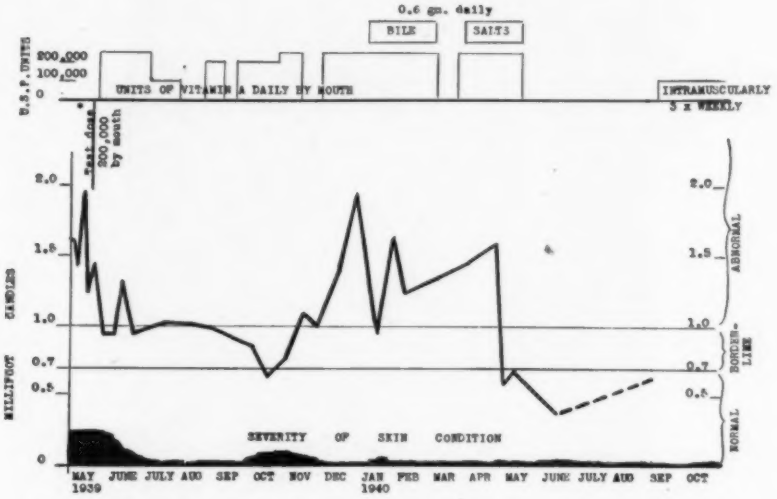
One of our patients, Case 2, a physician, carefully observed his progress while ingesting 60,000 to 100,000 units of vitamin A daily. Im-

provement began after one month and was fairly rapid on the trunk and upper extremities, although slower and incomplete on the lower extremities. The previously thickened skin became soft and pliable and ceased cracking in cold weather. The keratosis pilaris, which had always been present, disappeared. Also the patient particularly appreciated the absence of tingling and prickling, formerly felt after the bath. The surgical practice of this doctor required him to scrub his hands and arms with a brush several times a day and this had always provoked considerable discomfort. For relief after scrubbing, he regularly applied various creams to these areas and frequently also to other parts of the body, but after vitamin A therapy was instituted this greasing was discontinued and the previous discomfort from soap and water was no longer felt. The "snow storm" effect formerly present after bathing and undressing at night (due to marked desquamation at these times) was noticeably missing after treatment with vitamin A. Prior to the administration of vitamin A, perspiration was confined to his face, but now his hands perspire freely as well. This moisture of the hands is much more comfortable than the previous dryness. The only disadvantage in this improvement is considerable perspiration in the axilla, and, if not extremely careful, he is conscious of body odor, which he did not formerly experience. Also after treatment he noted a subjective "warmness of the skin so that he did not feel the cold weather very much" and a general "feeling of well-being." With continuous vitamin A therapy, these improvements were maintained without relapse during two winters. Finally, treatment was discontinued during four months this summer, and, despite the warm weather, there resulted a recrudescence of the old symptoms, which are now again responding to vitamin A.

One boy in this series, Case 1, had long presented in both axillae dry, yellowish, acuminate keratoses, which desquamated, leaving normal axillary skin as early as two weeks after beginning treatment. One woman, Case 3 (the wife of another physician), had never experienced any improvement, even in very warm weather. However, after several months of vitamin A injections she stated her skin was better than it had ever been in her memory and that friends who did not know she was taking treatment noticed the difference.

We had various results in respect to the route of vitamin A administration. In the physician the improvement was obtained by oral therapy alone and in three other patients, by intramuscular injections alone. The patient in Case 3 did not respond to oral administration of vitamin A but improved considerably with intramuscular injections. A similar experience in avitaminosis A has been reported by Edmund and Clemmesen[23] and by others cited by them and may be due to defective absorption of vitamin A from the gastrointestinal tract. The patient in Case 1, treated during two consecutive winters, obtained a considerable cutaneous improvement the first year with oral administration of vitamin

A. The second year the results were disappointing when intramuscular injections alone were employed. An obvious factor that might explain this result was that approximately five times as many units of vitamin A in the same period of time were taken the first winter orally as



*See Fig. 2.

Fig. 1 (Case 1).—Curve plotted from biophotometric observations during approximately one year of vitamin A therapy, showing seasonal variations in photometric test but relatively sustained skin improvement. Bile salts to promote absorption of the vitamin A were ineffectual in improving visual dysadaptation.

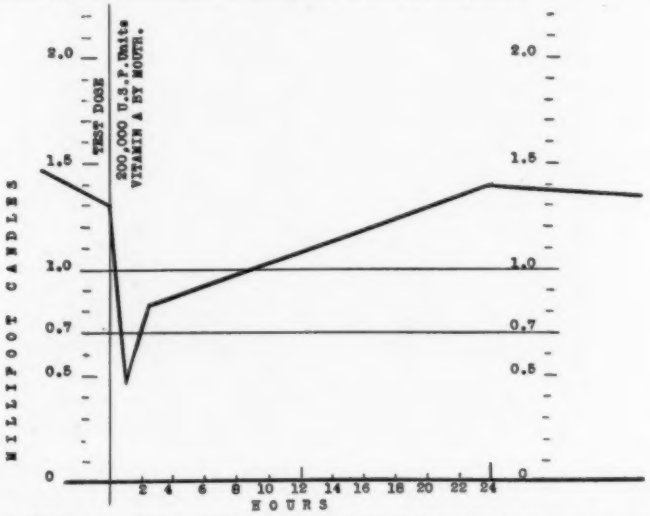
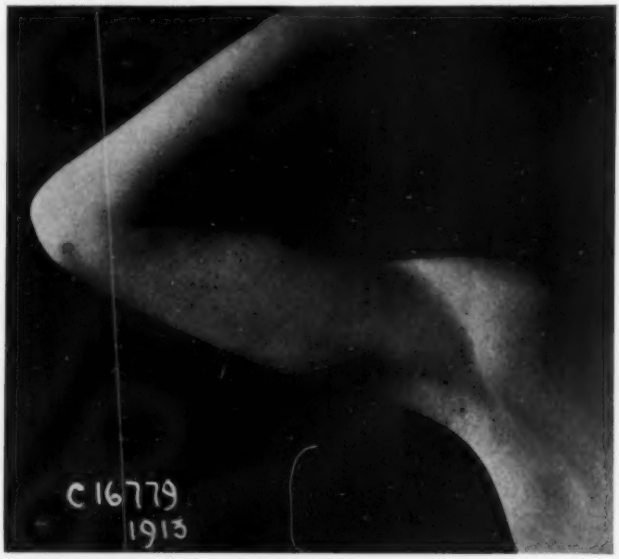


Fig. 2 (Case 1).—Curve showing results of biophotometric tests before and one, two, and twenty-four hours after initial dose of 200,000 international units of vitamin A by mouth.

were feasible the second winter with intramuscular injections. However, there have been reported many possible disturbances in the chain of vitamin A metabolism, which begins with ingestion at one end and progresses through digestion, absorption, conversion, storage, transporta-

Fig. 3 (Case 6).—Leg illustrating both typical polygonal scales and keratotic plugs projecting from the hair follicles below the knee.

tion, and so on to finally, at the other end, utilization of the vitamin A by the retina and other epithelial tissues. Destruction or incomplete utilization after absorption or even after intramuscular injection are conceivable. As a result, the mechanism of the vitamin A deficiency may vary from patient to patient. We therefore report our various



A.

B.

Fig. 4 (Case 1).—*A*, axilla before treatment, demonstrating keratoses long present, which desquamated off two weeks after beginning vitamin A therapy. *B*, same area after treatment, showing normal axillary skin.

observations in regard to the route of administration, and we believe that any superficial inconsistency from patient to patient is not surprising, even in the light of our present knowledge of the manifold varieties of disturbance of vitamin A metabolism.[24]

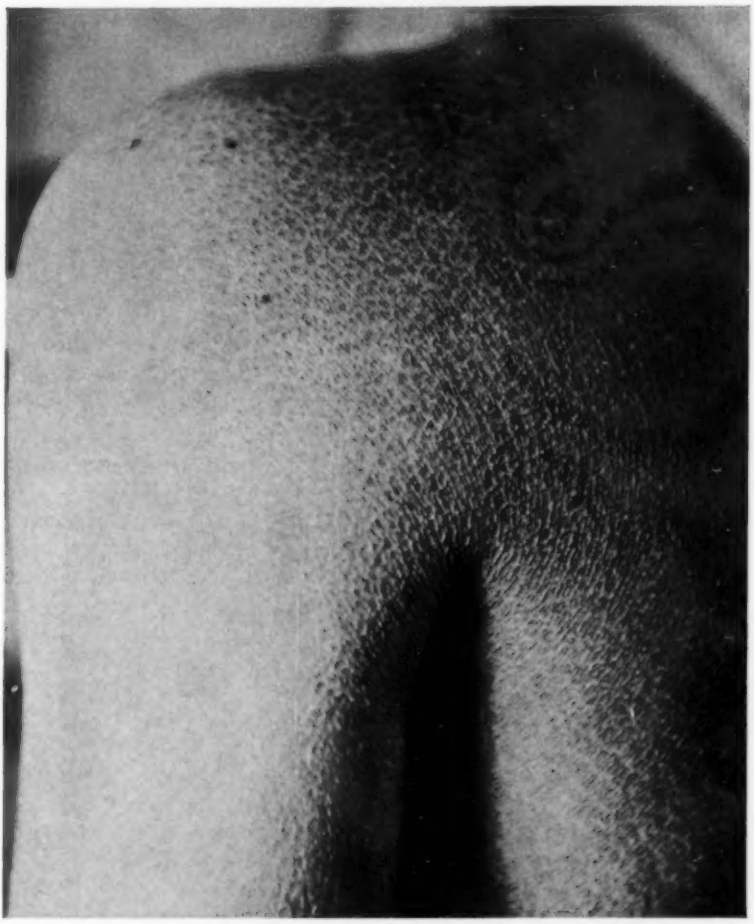


Fig. 5 (Case 4).—Shoulder showing typical polygonal scales of ichthyosis.

The question of course arises as to whether these encouraging results, consisting of both improved adaptation and cutaneous betterment, indicate that ichthyosis is due to an hereditary disorder in vitamin A metabolism. We believe our results indicate that at least in our patients vitamin A deficiency was an etiologic factor. However, since we did not obtain a completely normal skin, we do not exclude other contribu-

tory factors. Nevertheless, as a result of our experience with these patients, we believe that vitamin A therapy, with large doses over prolonged periods, is definitely indicated in ichthyosis.

THE SEASONAL FACTOR IN ICHTHYOSIS

With one exception, all of our patients with ichthyosis exhibited a marked cyclical variation in the condition of their skin. In summer they improved or became practically normal, while in winter they were at their worst. This spontaneous seasonal variation was not a factor in the improvement of our patients. We timed our therapeutic test so that our results were obtained during the winter. However, those patients who did not previously have a complete remission during the summer were also benefited by vitamin A during warm weather. Our one patient, who had never experienced any seasonal improvement, was definitely benefited by intramuscular injections. The only possible factor in the results obtained in this patient was vitamin A.

The spontaneous seasonal ebb and flow of the state of the skin in ichthyosis is synchronous with the observed seasonal variation of other phenomena definitely associated with vitamin A. Thus the generally accepted cutaneous manifestations of vitamin A deficiency[12, 13] show the same curve of seasonal variation in severity as ichthyosis. The data of Sweet and K'ang[25] on the month of onset of symptoms of vitamin A deficiency in 177 cases in China showed a marked peak in January, February and March, which was attributed to the deficient winter diet. Pett[20] and also Jeans, Blanchard, and Satterthwaite[18] have reported a fluctuation in the response to photometric tests for impaired dark adaptation with an increased incidence of subnormal results during the winter. The latter group believed that their results were related more closely to the occurrence of infections during the winter than to seasonal variation in diet. We suggest that there may be also an increase in the requirement for vitamin A in cold weather. Finally, Yudkin[26] reported estimations of vitamin A and carotene in the blood of normal persons and stated that although the number of cases was too small to draw any definite conclusions, it was of interest that those estimated in February and March were, in general, lower than those done in the autumn, a possible seasonal effect. Thus we see that various observers have recorded seasonal effects in various phenomena definitely associated with vitamin A, and these effects are synchronous with the seasonal changes of the skin in ichthyosis. This correlation is in harmony with our belief that vitamin A deficiency is an important etiologic factor in ichthyosis.

THE HEREDITY FACTOR IN ICHTHYOSIS

In all except one of our patients heredity played a conspicuous role. For example, the maternal uncle of one boy had ichthyosis. Another boy had two siblings with mildly ichthyotic skins and five other siblings

TABLE I

SUMMARY OF CASES OF ICHTHYOSIS TREATED WITH VITAMIN A

CASE NO.	INITIALS	AGE (YR.)	SEX	FAMILY HISTORY	SEASONAL VARIATION	BASAL METABOLIC RATE (%)	VITAMIN A TREATMENT				SKIN LESIONS SEVERITY		BIOPHOTOMETER TEST MILLIFOOT CANDLES OF LIGHT		COMMENT
							ROUTE	DOSE		DURATION OF TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	
								UNITS	FREQUENCY						
1	D. A.	13	♂	+	+	....	Oral	200,000	Daily	1 Year	+++	+	1.3–1.9†	0.38	I. M. route ineffective
							I.M.*	100,000	3 Weekly	4 Months					
2	M. S.	49	♀	–	+	....	Oral	100,000	Daily	2 Years	+++	+	....	....	
3	E. S.	33	♀	+	–	–20, –30	Oral	150,000	Daily	5 Months	+++	+	1.2	"normal"‡	Oral route ineffective
							I. M.	100,000	3 Weekly	8 Months					
4	R. K.	15	♂	+	+	–4, –13 –8	I. M.	100,000	2 Weekly	5 Months	+++	+	1.24	0.35	
5	E. O.	13	♀	+	+	....	I. M.	100,000	2 Weekly	3 Months	+++	+	1.2	0.69	
6	R. O.	11	♀	+	+	....	I. M.	100,000	2 Weekly	3 Months	++	+	1.6	0.58	Sister of E. O.

*I.M. signifies intramuscular injection.
†See Figs. 1 and 2 for complete data on Case 1.
‡Method of determination unknown.

completely normal. Two patients were sisters, whose paternal grandfather and a cousin on the father's side had a similar skin condition. The physician's wife stated that her brother and sister have had ichthyosis since birth and that another sister died at the age of 3 days because of ichthyosis congenita. Because of this frequent occurrence of multiple cases in a family, the hereditary nature of ichthyosis is generally accepted by students of both genetics and medicine.

This established hereditary transmission of ichthyosis, however, in no way excludes the possible importance of vitamin A as an etiologic factor. On the contrary, the basis of ichthyosis may be some hereditary disorder of vitamin A metabolism. Such a mechanism apparently is present in follicular keratosis (Darier's disease), which is hereditary at least in some cases, but according to Peck, Chargin, and Sobotka,[27] it is due to vitamin A deficiency and is cured by vitamin A therapy. Similarly in phrynoderma, which is also caused by vitamin A deficiency and relieved by treatment with vitamin A, we have noticed a familial occurrence. In our previous paper[13] we suggested that the explanation for multiple cases in a family might be some hereditary disturbance in vitamin A metabolism, interfering with the utilization of vitamin A or producing an increased minimal requirement for this substance.

SUMMARY AND CONCLUSIONS

1. Six individuals with ichthyosis obtained an improvement of their skin after prolonged treatment with large doses of vitamin A.

2. Five of these patients, who were examined by photometric test, had dark dysadaptation, which also improved with the administration of vitamin A.

3. The vitamin A deficiency in our patients was an important etiologic factor.

4. The basis of ichthyosis may be some hereditary disorder of vitamin A metabolism.

5. We believe that prolonged intensive treatment with vitamin A is definitely indicated in ichthyosis.

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7 WEST 96TH STREET
27 WEST 96TH STREET
247 WEST 99TH STREET

MATCH TEST

HERMANN VOLLMER, M.D., WITH THE COOPERATION OF HENRY W. HYSLOP,* M.D., AND HARRY V. LOMANT,† M.D.
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FOUR years' experimentation of applying the patch test principle to other test substances has been on the whole unsuccessful. Diphtheria toxin, various allergens, trichophyton, and saccharomyces concentrates have been tried on individuals reacting positively to these substances when applied intracutaneously. With the few well-known exceptions of contact dermatitis, even highest concentrations did not elicit skin reactions. Most unsuccessful were experiments with diphtheria toxin in concentrations as high as 15,000 minimal lethal doses per cubic centimeter. Strongly positive reactors to the Schick test were, without exception, negative to the patch test when such high concentrations of diphtheria toxin were applied. As early as 1932, Besredka[1] recognized the innocuity of diphtheria toxin applied to the uninjured skin ("immunité locale"). Attempts of Zamkin,[2] as well as of Cohen and Bruce,[3] using much lower toxin concentrations, were likewise unsuccessful.

For unknown reasons, these test substances do not penetrate the skin surface or, if they do, do not reach the reacting cells and capillaries of the epidermis. The stratum Malpighi seems to be the most reactive epidermal layer. It may be reached directly or indirectly via the lymphatics from either more superficial or deeper cutaneous layers. The two usual methods for introducing test substances into this epidermal region are the scratch test, with its various modifications, and the intracutaneous injection. At present, the intracutaneous test is preferred because it is quantitative, and consequently, as the result of using greater quantities, more positive reactions are obtained than with the scratch test. However, Schick[4] called attention to the fact that this greater percentage of reactors also includes pseudoreactors. An important study of the U. S. Public Health Service, recently carried out by Furcolow and coworkers,[5] revealed a surprising percentage of pseudoreactions to high concentrations of purified protein derivative. The frequency of such pseudoreactions seems to be underrated and consequently an obvious disadvantage of the intracutaneous test erroneously interpreted as an advantage. Moreover, intracutaneously injected substances occasionally enter the capillaries of the epidermis and corium and therefore cause systemic reactions more frequently than the properly performed scratch test.

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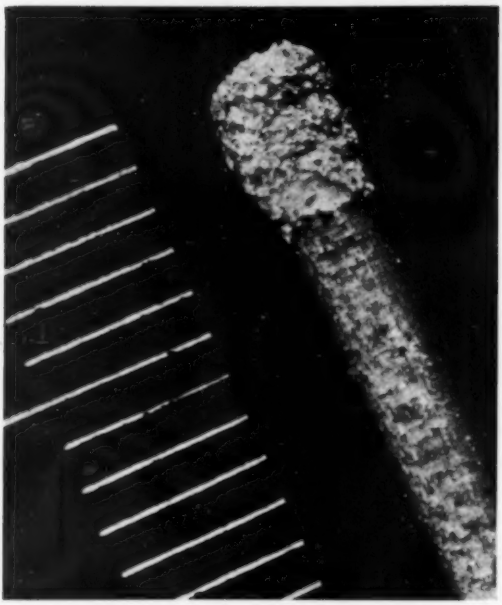

Fig. 1.—Magnified head of a match test showing the pumice particles attached to a wooden applicator.

Fig. 2.—The match test is placed perpendicularly on the stretched skin, and two or three turning movements are carried out between the index finger and the thumb.

Taylor[6] demonstrated that a strictly intracutaneous injection usually infiltrates the corium and the subcutaneous tissue, and that it is rather an exception than a rule that such an injection is actually localized into the epidermis. If the stratum Malpighi and its adjacent epidermal cells are to be reached, it appears to be more feasible to approach this region from the outside by abrading the stratum corneum. The sharp point of a needle used for scratch testing cuts or tears rather than abrades the stratum corneum and frequently also severs and penetrates the capillaries of the stratum Malpighi or even deeper capillaries. The result is bleeding. The risks are systemic reactions or, on the other hand, removal of the test substance by the blood flow.

Von Pirquet's[7] ingenious method avoids these disadvantages. The Pirquet needle ("bohrer") is not pointed but ends with a rather dull edge 3 mm. long, and is thus adapted to abrading the stratum corneum by turning movements. The weight of the instrument determines and equalizes the amount of pressure exerted. The injury is minimal, and bleeding is avoided if the abrasion is properly carried out.

The following is an attempt to simplify von Pirquet's method by combining a skin abrasive with the test substances. A suitable material must be an effective but smooth abrasive, harder than the keratin of the stratum corneum, and at the same time a powerful absorbent. Emery, carborundum, marble, quartz, glass, and diamond particles were tried and found unsatisfactory. Pumice is ideal. It is a porous, volcanic scoria consisting of parallel fibers, rich in capillary spaces, and thus an effective abrasive as well as a powerful absorbent.

METHOD

Pumice particles having a diameter of about 0.1 mm. are attached to the ends of wooden applicators 8.2 cm. long with Duco cement in such a way that only the proximal parts of the particles are embedded and their capillary spaces filled with the cement substance. The free ends of the pumice particles do not come into contact with the cement and thus retain unimpaired absorbent capacity. After complete drying of the cement, the head of the applicator containing the firmly attached pumice particles is dipped into the test substance. This simple instrument resembles a match and may be called match test.*

As shown in Fig. 1, the head of the match test is about 3.5 mm. long and its top has a slightly convex surface 2.5 mm. in diameter. The width of this surface prevents deeper penetration of the epidermis and bleeding. The skin of the inner surface of the forearm is stretched, the match test perpendicularly placed on the skin, and, under very slight pressure, two or three turning movements are carried out between the index finger and thumb (Fig. 2). This accomplishes a rather painless, scarcely visible abrasion of the stratum corneum, resulting in a circular area about 2 mm. in diameter where the originally dull appearance of

*Made available for investigational use by E. R. Squibb & Sons, New York, N. Y.

the uninjured skin turns into a more shiny, pink-brown spot. Microscopic transudation from intracellular spaces may take place following this abrasion.

As has been beautifully demonstrated by McMaster,[8] every injury, pressure, or abrasion of the skin permits entrance of foreign substances into the lymphatics and simultaneously increases the permeability of the lymphatic walls. It therefore may be expected that the minute abrasion carried out with the match test enhances the entrance of the accompanying test substance into the lymphatics; it may also increase the ecchymosis through the lymphatic walls and thereby the distribution of the test substance within the epidermal tissue.

Dry test substances might dissolve in the transudate of the abraded area, as shown by McMaster with dry dye particles, but their absorption would at least be greatly delayed. Therefore moist test substances should be used. Since glycerin is hygroscopic as well as a good preservative, glycerinated test substances have a double advantage and were exclusively used in this study.

For specific purposes the use of dry substances may be desired. It is known that smallpox vaccine remains permanently stable when the virus is kept in a dry condition. A mixture of smallpox vaccine and pumice powder may be dried in the vacuum or lyophilized and then attached with cement to the end of wooden applicators. A vaccination with such a permanently stable dry smallpox applicator must be carried out through a drop of water placed on the skin with a pipette. Thus the dry virus becomes redissolved and virulent.

It has been considered that chemical or biologic interaction between the various substances used in the match test could interfere with its efficacy. This, however, is not the case. First, Duco cement seems to be nonallergenic. Controls without allergens never elicited skin reactions. Second, the match test without test substance can easily be sterilized by heat as well as by alcohol without impairing the fastness of the wood-cement-pumice connection. Third, Duco cement is not soluble in glycerin or in water, the common solvents of the test substances. Finally, neither pumice nor cement seems to interact chemically with the used test substances. One possible exception is diptheria toxin, the stability of which is limited in the match test. But diphtheria toxin is unstable in any case, chiefly due to oxidation and sensitivity to light. It is by no means certain that cement or pumice exerts any destructive influence.

It is understood that in storing prepared match tests, care must be taken to prevent contact between the individual match tests as well as between the matches and the wall of the package (Fig. 3) in order to avoid loss of effective test substance. Also, generally adopted precautions for the storage of the individual substances remain imperative when they are used in connection with the match test. Smallpox match tests, for example, must be kept in the refrigerator when the common vaccine

is used. On the other hand, room temperature and humidity do not seem to interfere with the stability of glycerinated allergens.

Every match test should be used only once, even though a second use may often be successful. The abrasive capacity as well as the amount of available test substance is diminished by a single application, and weaker reactions, if any, result from repeated use.

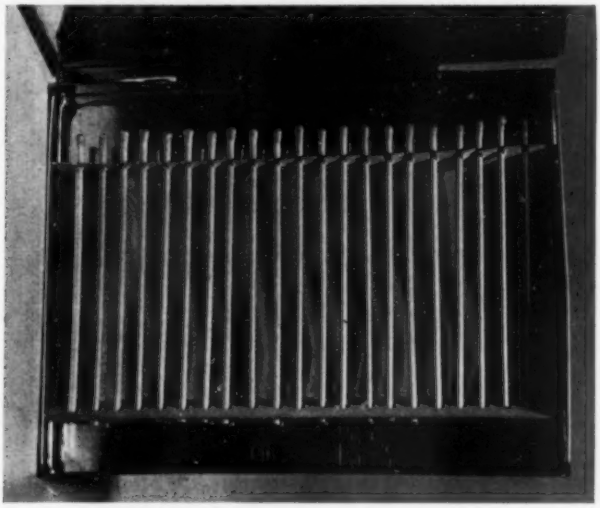

Fig. 3.—Carton containing match tests.

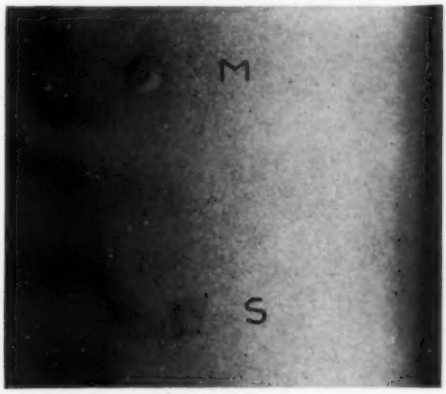

Fig. 4.—Weak skin reactions to June grass allergen. The reaction to the match test (*M*) is more definite than that to the scratch test (*S*).

The skin reactions to the match test (Figs. 4 and 5) resemble in most respects those elicited by the conventional scratch test. Since the match test forms a circular skin abrasion and the scratch test a longitudinal

skin abrasion, a more circular wheal formation results from the former, a more oval from the latter. Consequently one diameter of the scratch test wheal may be greater than the corresponding diameter of the match test reaction. This cannot justifiably be interpreted as a superiority of the scratch test.

Fig. 5.—Strong skin reactions to ragweed allergen. Match test (*M*), scratch test (*S*), and control (*C*) have been carried out simultaneously. The photograph illustrates the reactions after seven minutes.

The following technical mistakes in carrying out the match test may lead to failure or objectionable results:

1. Too few turning movements without pressure do not sufficiently abrade the skin. Weak or false negative reactions may result.
2. The match test not strictly perpendicularly placed on the skin may slip and fail to cause an abrasion.
3. Too many turning movements, exerting too much pressure upon the skin, cause too deep an abrasion. The skin reaction may be satisfactory, but the injury to the skin remains visible for two weeks or longer.
4. The test substances may be rendered ineffective by the length of storage or by disregard of storage precautions.

COMPARATIVE RESULTS

This preliminary evaluation of the match test was carried out in individuals known to be positive reactors to the intracutaneous or scratch test. In only few instances were the different tests done simultaneously. Most of the tests were performed by residents and nurses not yet familiar with this form of test. Occasional technical mistakes may therefore be anticipated.

I. Diphtheria Toxin

Schick,[9] in 1908, described positive skin reactions following the application of a diphtheria toxin concentrated ten times to the scarified skin. He observed the frequent occurrence of purulent pustules in the center of positive reactions which he ascribed to the action of the toxin rather than to secondary infections. Reh,[10] using a diphtheria toxin containing 2,500 minimal lethal doses per cubic centimeter, confirmed Schick's findings. Mérieux[11] abraded the skin by vigorous friction with dry gauze and rubbed into this area a glycerinated diphtheria toxin containing 5,000 minimal lethal doses per cubic centimeter. Positive reactions resulted in Schick-positive individuals. Grozin[12] rediscovered the diphtheria scratch test thirty-one years after Schick's[9] original publication.

In the present study, match tests were dipped into glycerinated diphtheria toxin containing 15,000 and 7,500 minimum lethal doses, respectively, per cubic centimeter. They were stored in cartons in a cool place and used various lengths of time after their preparation.

In thirty patients, including twenty-five positive and five negative reactors to the intracutaneous Schick test, there was agreement with the match test, except for one child having a positive Schick and a negative match test reaction. In this series the match tests were used within thirty days following their preparation. Another series of children tested with older match tests gave unsatisfactory agreement with the Schick test, indicating that the diphtheria toxin deteriorated. Besides, minute central pustules and subsequent necroses resembling those described by Schick[9] occurred in some of the positive reactors. They probably are due to the primary toxic effect of the diphtheria toxin rather than to secondary infection and result in objectionable discoloration of the skin. The main drawback, however, seems to be that cutaneous diphtheria toxin tests in general are not quantitative. The reaction to the quantitatively determined Schick test proved to be a significant though not infallible criterion for the susceptibility to diphtheria. It might be questioned whether the Schick test is sufficiently quantitative as compared with direct titration of the blood. Unquestionably, every departure from the quantitative principle is problematic, in the diphtheria toxin test more than in any other skin test.

Conclusion.—Match tests freshly prepared with glycerinated diphtheria toxin containing 7,500 or less minimal lethal doses per cubic centimeter produce skin reactions satisfactorily agreeing with the Schick test. Though simpler, the diphtheria toxin match test is, for biologic reasons, not as acceptable as the Schick test and should be resorted to only when the latter is not practicable.

II. Tuberculin

Match tests were impregnated with old tuberculin made in 1937 by the New York Department of Health, and the prepared tests were stored in cartons at room temperature.

Fifty-one tuberculous children who were positive reactors to the patch test, as well as to the Mantoux test with 0.1 mg. of old tuberculin, were tested. Among them, forty-eight showed a positive and three a negative reaction to the match test. Storage for several months did not seem to change appreciably the potency of the tuberculin match test.

Conclusion.—The tuberculin match test seems to be equivalent to the Pirquet test, as was to be expected. It has no advantages over the tuberculin patch test which in previous studies[13] proved to be superior to the Pirquet test.

III. Smallpox Vaccine

Match tests were prepared with smallpox vaccine and kept in glass tubes in such a way that the wooden end of the applicator was stuck into the cork and the head of the match test did not touch the walls of the glass tube (Fig. 6).

Fig. 6.—Match test prepared with smallpox vaccine is kept in a sterile glass tube.

There was a take in twenty-one of thirty-two vaccinated children. This seems to be a poor result. However, if we analyse the negative results, we arrive at a more favorable evaluation. It was revealed that in one hospital the prepared smallpox match tests were kept at room temperature throughout the day and only at night were kept in the icebox. If we regard this as a neglect of the storage precautions and eliminate these children as well as those vaccinated with match tests correctly stored for more than three weeks, only three children remain who failed to take.

Since fluid smallpox vaccine is known to deteriorate, match tests were prepared with the dry powder of lyophilized smallpox vaccine. Ten children were vaccinated through a drop of water with these dry smallpox match tests; not one child reacted. Whether this lyophilized smallpox virus was potent, I am not able to state. These experiments are being continued.

Conclusion.—Smallpox vaccinations can successfully be performed with the match test if the proper storage precautions are not neglected. A permanently stable dry smallpox match test remains a possibility though the present experiments were unsuccessful.

IV. Allergens

Match tests were prepared with glycerinated extracts of ragweed, June grass, orris root, egg white, and house dust, respectively, and stored for up to five months at room temperature. In order to concentrate the allergens on the top of the match test head, the applicators were kept for one day after their impregnation with their heads inclined in a downward position.

Forty-seven individuals who previously had shown a positive intracutaneous or scratch test reaction to the same allergen were tested with the match test. All reacted positively. Some reactions appeared after three minutes, most of them after from five to ten minutes; few were delayed up to thirty minutes. Storage for three months did not appreciably diminish the activity of the match tests.

Conclusion.—Match tests prepared with glycerinated allergens proved to be very reliable. None of forty-seven positive reactors to the intracutaneous test or scratch test failed to react to the match test.

SUMMARY AND CONCLUSIONS

The superiority of the intracutaneous test over the scratch test is questioned. The quantitative principle and the higher percentage of positive reactors appear to be advantages. However, this may be an erroneous evaluation if the fact of misleading pseudoreactions and the risk of systemic reactions following intracutaneous injections are considered. Whenever greater amounts of test substances are intracutaneously injected than are usually absorbed in the scratch test, the risk of pseudoreactions seems to rise with increasing concentrations of the test substance. The quantitative principle applied with the Schick test, however, appears to be essential and indispensable inasmuch as an intracutaneous titration of the antibody concentration is aimed at.

Some physiologic facts relating to skin tests are outlined, and the ingenuity of von Pirquet's abrasion method is appreciated.

The match test represents a simplification of von Pirquet's cutaneous test by combining a skin abrasive with the test substances. The match test resembles a match, the head of which consists of fine pumice powder attached by a cement substance to one end of a wooden applicator.

Pumice is a smooth abrasive as well as a powerful absorbent and does not seem to interact chemically with the test substances used in this study. Two to three turning movements with the match test perpendicularly placed on the stretched skin accomplish a rather painless abrasion of the stratum corneum and carry the accompanying test substances into the reactive epidermal cell layers.

Allergy match tests prepared with glycerinated ragweed, June grass, orris root, egg white, and house dust allergens elicited distinctly positive reactions in forty-seven patients known to be positive reactors to intracutaneous or scratch tests with the corresponding allergens. No systemic reactions occurred.

The tuberculin match test proved to be practicable and equivalent to the Pirquet test.

Smallpox vaccinations can successfully be performed with the match test when proper storage precautions are observed. A permanently stable, dry smallpox match test remains a possibility, though the present experiments were unsuccessful.

Match tests freshly prepared with diphtheria toxin concentrates produced skin reactions satisfactorily agreeing with the Schick test. The stability of this preparation is limited.

Numerous advantages were experienced with the match tests. Children are amused rather than frightened when the match test is applied, and even the most apprehensive individuals do not object. Obviously, a wooden applicator is mentally less associated with pain than a syringe or metal instrument. Actually pain is almost entirely avoided. No systemic reactions seem to occur. The preparation is always ready for use, and its ease of application renders skin testing a more casual and simple procedure.

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A MODIFIED OR REVERSE SCHULTZ-CHARLTON TECHNIQUE IN THE DIAGNOSIS OF SCARLET FEVER

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THE diagnosis of "observation scarlet fever" is applied to a significant number of patients entering the contagious disease unit of Queens General Hospital. This diagnosis implies that the patient presents enough of the signs of scarlet fever to warrant admission to a hospital for contagion, and yet not sufficient signs definitely to establish the diagnosis. The history of a recent rash and sore throat is frequently obtained. At the onset of scarlet fever, the findings may be so meager that a definite diagnosis cannot be made. In such instances, the patient may be held in quarantine for two or three weeks while awaiting the appearance of desquamation to aid in the diagnosis. At the end of this period, the diagnosis may still remain in doubt. The experiments described below were directed initially toward the clarification of this type of case.

The Schultz-Charlton test, as originally described,[1] consists of the injection of convalescent scarlet fever serum into the skin of a patient with an equivocal rash. Local blanching of the rash at the site of injection is considered diagnostic of scarlet fever. At present, antitoxin is used for the test in order to increase its specificity. A negative Schultz-Charlton test does not exclude the diagnosis of scarlet fever.

The ability of convalescent serum to blanch the scarlet fever rash apparently depends on the presence in the serum of the specific antitoxin which neutralizes the scarlatinal toxin locally.[2] According to Haselhorst[3] and Schultz-Charlton,[1] appropriate antitoxin levels for the production of this phenomenon are developed during the second or third week after the onset of symptoms of scarlet fever. If this blanching ability in the serum of a patient during the course of an undiagnosed illness could be demonstrated on a known scarlatinal rash, the diagnosis of scarlet fever could be made with reasonable certainty. This principle was advanced by early investigators of the Schultz-Charlton test.[3]

The purpose of this paper is to describe a method which has been used in the diagnosis of certain doubtful cases of scarlet fever. This method may be further extended to investigate some of the various immunologic aspects of the disease.

This work was carried out in the Pediatric and Contagious Wards of the Queens General Hospital with the kind permission of Dr. Henry Reisman, Director of the Service, to whom we express our appreciation.

TECHNIQUE

On entry of the patient into the hospital, 5 c.c. of blood were withdrawn under sterile precautions. The serum was separated and placed in labeled vials. This procedure was repeated at varying intervals during the hospital stay, usually at fourteen and twenty-one days after the onset of the illness. The sera were kept in the refrigerator until

TABLE I

REVERSE SCHULTZ-CHARLTON TEST IN SCARLET FEVER CASES

CASE NO.	NAME	AGE (YR.)	SEVERITY OF DISEASE	DICK*	BLANCHING POWER OF SERUM			CONTROL†
1	F. S.	4	Moderately severe	Neg.	4th day—Neg.‡	15th day—Neg.	21st day—3+	3+
2	J. G.	10	Mild	Neg.	5th day—Neg.	17th day—2+	20th day—3+	3+
3	H. F.	4	Mild	Neg.	3rd day—Neg.	16th day—Neg.	22nd day—2+	3+
4	M. H.	6	Moderately severe	Pos.	4th day—Neg.	16th day—Neg.	22nd day—Neg.	3+
					4th day—Neg.	16th day—Neg.	22nd day—1+	4+
5	W. D.	5	Moderately severe	Pos.	5th day—Neg.	15th day—Neg.	21st day—2+	2+
6	K. Z.	6	Moderately severe	Neg.	2nd day—Neg.	14th day—1+	21st day—2+	3+
7	J. A.	6	Moderately severe	Neg.	3rd day—Neg.	14th day—1+	21st day—2+	2+
8	P. D.	14	Mild	Neg.	3rd day—Neg.	14th day—2+	21st day—2+	2+
9	T. T.	7	Moderately severe	Neg.	2nd day—Neg.	14th day—Neg.	21st day—Neg.	1+
					2nd day—Neg.	14th day—Neg.	21st day—2+	2+
10	J. L.	8	Moderately severe	Neg.	3rd day—Neg.	14th day—Neg.	21st day—2+	2+
11	A. S.	6	Moderately severe	Neg.	3rd day—Neg.	15th day—Neg.	22nd day—Neg.	1+
					3rd day—Neg.	15th day—Neg.	22nd day—2+	2+
12	A. H.	3	Mild	Neg.	2nd day—Neg.	14th day—2+	21st day—2+	2+
13	F. G.	4	Moderately severe	Pos.	2nd day—Neg.	14th day—1+	21st day—1+	2+
14	A. P.	29	Severe	Pos.	3rd day—Neg.	14th day—Neg.	21st day—2+	2+
15	H. R.	7	Severe	Neg.	2nd day—Neg.		21st day—2+	2+
16	M. D.	8	Moderately severe	Neg.	2nd day—Neg.		21st day—2+	1+
17	J. Z.	4	Moderately severe	Neg.	6th day—Neg.	14th day—1+	21st day—2+	2+
18	L. R.	3	Severe	Neg.	3rd day—Neg.	15th day—Neg.	21st day—3+	Neg.
19	G. H.	7	Moderately severe	Neg.	3rd day—Neg.	16th day—Neg.	21st day—2+	Neg.

*The Dick test was done on admission. With one exception this was during the first week of illness. Case 20 was Dick tested on the 8th day.

†The control is an ordinary Schultz-Charlton test using scarlatinal antitoxin as the blanching agent.

‡Refers to the day of illness on which serum was collected.

the complete series was obtained from the patient. The entire series was then used for blanch tests on another patient with a definite heavy, early scarlatinal rash. At the same time a Schultz-Charlton test was performed for comparative purposes with the specific antitoxin dispensed by the laboratory of the New York City Department of Health. In all instances, 0.2 c.c. was injected intradermally so that quantitative estimates of the blanching reaction might be made. These were graded from 1+ to 4+.

Thus a rash, definitely diagnosed as scarlet, was used to determine the unknown blanching power of sera, the exact reverse of the original Schultz-Charlton procedure. For convenience, this technique was termed the reverse Schultz-Charlton test.

MATERIAL

Sera from the following were tested by the above described technique:

1. Nineteen patients with scarlet fever of varying grades of severity.
2. Five patients with observation scarlet fever.
3. Eight patients with nonscarlatinal hemolytic streptococcus infections.

The results are shown in Tables I, II, and III.

TABLE II

REVERSE SCHULTZ-CHARLTON TEST IN OBSERVATION SCARLET FEVER CASES

CASE NO.	NAME	AGE (YR.)	DICK	BLANCHING POWER OF SERUM			CONTROL*
20	P. S.	30	Pos.	8th day—Neg.	13th day—1+	20th day—2+	4+
21	A. V.	6	Pos.	6th day—Neg.	13th day—Neg.	20th day—2+	3+
22	S. S.	28	Neg.	6th day—2+	14th day—Neg.	20th day—2+	2+
23	B. M.	6	Neg.	4th day—2+		21st day—2+	3+
24	E. G.	20	Neg.	6th day—3+		24th day—3+	3+

*The control is the ordinary Schultz-Charlton test using scarlatinal antitoxin as the blanching agent.

TABLE III

REVERSE SCHULTZ-CHARLTON TEST IN MISCELLANEOUS STREPTOCOCCUS INFECTIONS

CASE NO.	NAME	AGE (YR.)	DISEASE	BLANCHING POWER OF SERUM		CONTROL
25	J. O.	2	Purulent otitis media	3rd day—Neg.	21st day—Neg.	2+
26	E. P.	2	Purulent otitis media	4th day—Neg.	21st day—Neg.	2+
27	D. C.	11	Purulent arthritis	14th day—Neg.	21st day—3+	2+
28	J. M.	1½	Sinusitis*	17th day—3+	34th day—2+	2+
29	T. G.	2	Purulent otitis media	9th day—Neg.	25th day—Neg.	3+
30	R. P.	1½	Purulent otitis media	†	30th day—Neg.	3+
31	P. V.	1½	Purulent otitis media	†	31st day—Neg.	3+
32	T. M.	5	Empyema‡	4th day—1+	21st day—1+	2+

*History of sore throat and rash seventeen days before admission to the hospital which probably was scarlet fever.

†No earlier serum was collected. However, if blanching power were developed at all during the illness, it should still be present at thirty days.

‡Received a transfusion before sera were collected.

ANALYSIS OF RESULTS

It will be noted that none of the sera collected on admission from patients with definite scarlet fever would blanch a scarlatinal rash. This conforms with the results of early workers.[1, 3] However, the sera collected on the fourteenth or, at the latest, on the twenty-first day of illness did possess this power. In a few instances it was necessary to retest the serum on an intense rash when it failed to blanch a moderately intense one (Cases 4, 9, and 11).

It will also be noted that the intensity of the blanching power does not correspond to the severity of the disease. It is not surprising, therefore, that the very patients who present diagnostic problems because of mild symptomatology may yield a strongly positive reverse Schultz-Charlton test.

It cannot be stated with certainty whether the extent of the intensity of the blanching parallels the antitoxin titer of the serum used in the test. An attempt to repeat Rane's modification of the Ramon flocculation[5] technique in order to estimate quantitatively the antitoxin level of the sera used was unsuccessful. This work is being repeated.*

The patients in Cases 20 and 21 were admitted with diagnoses of observation scarlet fever. With further clinical evidence obtained during their hospital stay, the diagnosis of scarlet fever was ultimately established. In both instances the development of the blanching power in their serum during the illness was demonstrated.

The patients in Cases 22, 23, and 24 were also admitted with diagnoses of observation scarlet fever, but after prolonged study, were discharged as "no case of contagion." There was no change in the blanching power of the blood of these patients during this period. It is significant to note that the sera of these patients had possessed blanching power during the early part of their illness. *This was never found in a case of scarlet fever.* The presence of blanching power in the serum of a patient during the first week of illness appears to be strong evidence *against* the diagnosis of scarlet fever. Apparently, if the patient has sufficient antitoxin in his serum to produce a positive blanch test, he is relatively immune to the disease.

COMMENT

The application of the reverse Schultz-Charlton technique to the diagnosis of scarlet fever may be simplified by an example. A patient is admitted for observation for scarlet fever. Blood is withdrawn on entry to the hospital and the serum tested for its ability to blanch a definite scarlet rash. If the patient's serum does blanch a scarlet rash on admission, he probably does not have scarlet fever. If his serum does not produce a blanch, further specimens of serum are collected on the fourteenth and twenty-first days, and also tested for their blanch-

*This work is being done by Miss M. Mollov of the Pathology Department of the Queens General Hospital.

ing power. If the latter sera give a positive blanch test, the diagnosis of scarlet fever is established. If they do not, the patient does not have scarlet fever. The latter half of the procedure is of limited practical value, since the diagnosis is made late in the disease. However, it may settle some of the many heated arguments that arise over problematic cases and thus give valuable information in the diagnosis of obscure cases.

The short series does not permit a dogmatic interpretation. However, in the group of cases we have tested, the conclusions drawn above have been consistent.

In the streptococcus hemolyticus infections other than scarlet fever, no *change in blanching power* of the serum was noted over at least a three-week period of illness. Though none of the patients in this group had a history of scarlet fever, those in Cases 27, 28, and 32 did have blanching power in their blood. It is well known that some individuals have immunity to scarlet fever without ever having had the disease clinically.

Further investigation of patients with streptococcus hemolyticus infection other than scarlet fever may yield interesting information. It is claimed by some that such an infection, if due to the scarlatinal streptococcus, may lead to immunity against scarlet fever. This may be detectable by the reverse Schultz-Charlton technique.

Our results with the Dick test have been disappointing. The Dick technique[6] was faithfully followed, using the material dispensed by the New York City Board of Health laboratories. In our experience, although a positive Dick test suggests a lack of immunity, a negative Dick test cannot be safely relied upon as indicating the presence of immunity. During the first week of scarlet fever when immunity is low, 80 per cent of our patients showed negative reactions to the Dick test. The blanching power of the patient's serum may constitute a more accurate test for selecting individuals who require immunization against scarlet fever. This, to be sure, is a more cumbersome technique and would only be applicable to a limited number of interesting cases. It would seem to be a very desirable test for individuals to be exposed, such as hospital attendants. The use of this technique is almost entirely limited to a contagious disease hospital where it is usually not difficult to find a good scarlet rash upon which to run the tests during a busy scarlet fever season.

SUMMARY

1. A clinical method in the diagnosis of scarlet fever is described, using a reverse Schultz-Charlton technique of testing unknown serum on a known scarlatinal rash.

2. This method was applied to patients with scarlet fever, to those with observation scarlet fever, and to those with nonscarlatinal streptococcus hemolyticus infections. The results are tabulated and discussed.

3. The possible application of this technique to estimate the degree of immunity to scarlet fever is suggested.

The authors had hoped to include a larger series to establish this hypothesis, but active duty with the Military Service made this impossible. We trust that this preliminary report will prompt a similar study on a larger service.

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THE ROLE OF HONEY IN THE PREVENTION AND CURE OF NUTRITIONAL ANEMIA IN RATS

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IT IS known that iron constitutes a part of the hemoglobin molecule and that copper is essential for the formation of hemoglobin.[14]

Honey contains both iron and copper. Table I shows the iron and copper content of honeys as found by various investigators.

There is no record of controlled experiments on the role of honey in hemoglobin formation. However, there are some indications that honey can contribute to the increase of the hemoglobin content of blood. Emrich[8] selected six groups of children, who were similar as to type, age, constitution, and hemoglobin content of blood, and who came mostly from the same family or from families with similar living conditions. There were two children in each group, of which one received honey and milk, the other milk only in addition to their normal diet. The results showed that those receiving honey had a greater increase in hemoglobin than those who did not receive this supplement. Rolleder[9] selected twenty-nine pairs of boys, the individuals of each pair being as far as possible similar in weight, stature, and the hemoglobin content of blood. One boy of each pair received two tablespoonfuls of honey daily for six weeks. The other boy served as control. At the end of a six weeks' period, there was a marked tendency for the blood of the boys who had honey in their diet to show an increase in hemoglobin content. Two-thirds of them showed an average increase of 8.5 per cent; two-thirds of the boys who did not have honey showed a marked fall in hemoglobin content of their blood. Presumably the remaining third in each case showed little change. A second test in which the controls were the experimental children and vice versa confirmed these results. In both cases there was no specification as to the kind of honey that was fed to the children.

The results are rather surprising, because the amount of iron in the honey consumed, computed on the highest basis, would amount only to about 0.1 mg. daily. This is only an insignificant part of the daily requirement.

We have conducted a series of controlled experiments on the value of honey in prevention and cure of nutritional anemia in rats. Because honeys differ in their iron and copper content, dark honeys being richer

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TABLE I

IRON AND COPPER CONTENT OF HONEYS

NAME OF THE INVESTIGATOR	IRON PER KILOGRAM			COPPER PER KILOGRAM		
	DARK HONEYS MG.	LIGHT HONEYS MG.	UNSPECIFIED MG.	DARK HONEYS MG.	LIGHT HONEYS MG.	UNSPECIFIED MG.
Schuette and Remy[10]	9.4	2.4		0.56	0.29	
Svoboda[12]	11.6			1.3		
Svoboda[13]	17.5			1.4		
Peterson and Elvehjem[8]			11.5			
Lindow and Elvehjem[6]						2.0
Elser[1]			3.3			
Elser[2]			2.25 to 9.27			

in those minerals, buckwheat honey, as a representative of the dark type, and sweet clover and basswood honey, as representatives of the light type, were used.

A. Role of Honey in Prevention of Nutritional Anemia in Rats.—

1. Unrestricted Feeding: Rats were weaned at 3 weeks of age. They were placed on a milk and honey diet. A milk and sucrose diet was fed to the controls. The milk was obtained from the University dairy herd. Twenty grams of honey were added to 80 c.c. of milk, but only 16 Gm. of sucrose were added to 84 c.c. of milk for the controls in order to equalize the energy intake per unit of food consumed. The rats were fed ad libitum. A record of food consumption was kept. Four rats were used in each group. The Newcomer method for the determination of hemoglobin was used. The average results of the four rats in each group of the experiment are presented in Table II.

TABLE II

ROLE OF HONEY IN PREVENTION OF NUTRITIONAL ANEMIA IN RATS (FED AD LIBITUM)

WEEKS OF DIET	DARK HONEY 20 PER CENT			LIGHT HONEY 20 PER CENT			SUCROSE 16 PER CENT		
	AVERAGE WEIGHT OF RATS (GM.)	HB.*	AVERAGE DAILY FOOD CONSUMED PER RAT (C.C.)	AVERAGE WEIGHT OF RATS (GM.)	HB.*	AVERAGE DAILY FOOD CONSUMED PER RAT (C.C.)	AVERAGE WEIGHT OF RATS (GM.)	HB.*	AVERAGE DAILY FOOD CONSUMED PER RAT (C.C.)
Initial	33	10.8	--	33	10.6	--	30	---	--
1	46	10.7	16	47	9.8	16	49	10.6	20
2	69	8.4	26	62	7.9	26	71	8.1	27
3	91	9.5	32	80	8.2	28	82	7.3	29
4	108	10.2	36	92	7.7	28	98	6.7	30
5	129	10.6	38	109	7.1	29	115	5.6	30
6	144	11.4	37	120	6.4	31	130	5.0	32
7	158	11.0	40	130	5.6	30	145	4.8	33
8	168	11.8	39	137	5.5	29	153	--	34
9	178	---	39	140	--	29	165	3.9	34
10	185	11.4	39	147	4.6	29	173	3.6	31

*Grams per 100 c.c. of blood.

TABLE III

ROLE OF HONEY IN PREVENTION OF NUTRITIONAL ANEMIA IN RATS (PAIRED FEEDING)

WEEK OF DIET	SUCROSE 16 PER CENT			LIGHT HONEY 20 PER CENT			SUCROSE 16 PER CENT			DARK HONEY 20 PER CENT		
	AVERAGE WEIGHT OF RATS (GM.)	HB.*	AVERAGE DAILY FOOD CONSUMPTION PER RAT (C.C.)	AVERAGE WEIGHT OF RATS (GM.)	HB.*	AVERAGE DAILY FOOD CONSUMPTION PER RAT (C.C.)	AVERAGE WEIGHT OF RATS (GM.)	HB.*	AVERAGE DAILY FOOD CONSUMPTION PER RAT (C.C.)	AVERAGE WEIGHT OF RATS (GM.)	HB.*	AVERAGE DAILY FOOD CONSUMPTION PER RAT (C.C.)
Initial	37	10.7	22	36	11.6	21	37	10.3	17	32	10.5	17
1	53	8.8	25	50	9.5	25	45	8.9	23	45	10.1	22
2	72	7.1	26	67	7.7	25	64	7.3	25	65	8.5	25
3	85	6.9	27	81	7.1	26	83	6.7	27	81	9.0	27
4	98	6.0	29	93	6.6	28	97	6.5	29	95	9.9	29
5	116	5.2	30	107	5.9	31	111	6.5	34	109	9.6	34
6	135	4.7	33	122	5.2	32	131	6.1	31	132	8.3	32
7	151	4.8	37	141	5.8	36	143	6.0	34	146	8.4	34
8	170	4.5	39	162	5.4	40	158	5.1	36	157	8.7	36
9	189	4.2	36	178	5.1	36	169	5.1	38	166	9.5	38
10	203	4.1	36	189	4.6	36	177	5.0	35	176	8.9	36
11	215	3.6	37	202	4.3	35	187	4.7	36	184	10.9	36
12	226	3.6	34	214	3.6	33	194	3.5	36	194	11.0	35
13	233	3.4	35	218	3.5	36						
14	242	3.1	33	224	3.8	33						
15	250	2.9	40	229	4.0	38						

*Grams per 100 c.c. of blood.

The table reveals that there was an increase in the hemoglobin content of the rats fed dark honey and a gradual decline of the hemoglobin content in the rats fed either light honey or sucrose. The gain in weight and the food consumption were the greatest in the rats fed dark honey.

2. Paired Feeding Method: Because the rats fed dark honey consumed more food, their iron and copper intake was also greater. In order to eliminate this difference, a paired feeding method was adopted.[7] Three-week-old rats were placed on the diet. A measured amount of the mixture was given to each of the paired rats, and the food left in the dish was measured the next morning. Each animal of the pair received then the amount consumed by one of them during the preceding day. In case the food was eaten by both animals, a 2 or 3 c.c. increase was made for the next day. Five pairs were used in the study of white honey and six pairs for the dark honey feeding.

The average results of the experiment are presented in Table III.

It is evident from the table that the dark honey diet supplied enough iron and copper to maintain the hemoglobin at about 90 per cent of the initial level for ten weeks, after which the value rose to normal while the hemoglobin content of blood of the rats fed white honey fell to nearly 30 per cent of the initial value and then maintained itself at about that level. There was a slight tendency towards an increase after thirteen weeks. The rats fed sucrose supplement showed a gradual fall in blood hemoglobin throughout the experiment without any tendency to increase at the close.

B. *Role of Honey in Curing Nutritional Anemia in Rats.*—The rats were prepared by the method of Elvehjem and Kemmerer.[4] They were then placed on raw whole milk diet, the milk being obtained from the University dairy herd. When the hemoglobin content of twenty rats fell to about 6 Gm. per 100 c.c. level, they were divided into ten paired groups. One animal in each group received dark honey and another light honey as supplement to milk. The rest of the animals were kept on the whole milk diet longer, until their hemoglobin was slightly above 4 Gm. per 100 c.c. level. They were then divided into five pairs and fed the same supplements.

Table IV shows the average results.

It is evident that in both cases there was an increase in the hemoglobin content of the blood of rats receiving dark honey as a supplement, while that of the rats receiving light honey continued to fall until it reached a level of about 3 Gm. per 100 c.c.

The average amount of iron and copper consumed by the rats daily can be considered satisfactory for the interpretation of the results obtained. Using the average iron content of dark honey shown in Table I, namely, 12.8 mg. per kilogram, and that of light honey, 2.4 mg. per kilogram, Table IV shows a computation of the probable amount of iron consumed by the rats from the honey in this study. It varied from 0.072

TABLE IV

ROLE OF HONEY IN CURING NUTRITIONAL ANEMIA IN RATS (PAIRED FEEDING)

WEEKS OF DIET	DARK HONEY				LIGHT HONEY			
	AVERAGE WEIGHT OF RATS (GM.)	HB.	AVERAGE DAILY FOOD CONSUMPTION PER RAT (C.C.)	MILLIGRAMS OF IRON CONSUMED DAILY WITH HONEY*	AVERAGE WEIGHT OF RATS (GM.)	HB.	AVERAGE DAILY FOOD CONSUMPTION PER RAT (C.C.)	MILLIGRAMS OF IRON CONSUMED DAILY WITH HONEY*
Higher Hemoglobin Start†								
Initial	77	5.6	--		75	5.8	--	
1	89	5.6	28	.075	85	5.0	26	.013
2	100	6.5	29	.078	95	4.4	28	.014
3	113	7.6	29	.078	107	4.1	27	.014
4	126	7.9	27	.072	114	3.7	25	.012
5	136	7.8	28	.075	127	3.4	26	.013
6	141	7.9	28	.075	133	3.2	26	.013
7	146	8.9	29	.078	141	3.1	27	.014
8	152	8.6	29	.078	143	3.0	26	.013
Lower Hemoglobin Start‡								
Initial	103	4.6	--		101	4.2	--	
1	116	4.6	30	.080	116	3.7	27	.014
2	128	5.0	30	.080	124	3.5	29	.015
3	149	4.6	34	.091	143	3.1	33	.017
4	153	5.9	33	.089	147	3.1	31	.016
5	156	6.3	31	.083	147	2.8	28	.014
6	159	7.0	31	.083	156	2.9	30	.015

*In making this computation, the figure 0.21 Gm. honey per cubic centimeter of food consumed was employed.

†During the eighth week, only five pairs remained in the experiment, the other being discarded because rats fed on light honey died.

‡During the sixth week, only two pairs remained in the experiment for the same reason.

mg. to 0.091 mg. daily for the dark and from 0.013 mg. to 0.017 mg. for the light honey. The copper intake of the rats from the honey can be assumed to be about one-tenth of these values based on the iron copper ratios shown in Table I, which is about the proportion required in the curative doses for anemic rats.[5] There was also some iron available from the milk. Smith and Otis[10] showed that a daily addition of 0.014 mg. of iron (as $FeCl_3$) brings about an increase of 1 Gm. of hemoglobin per 100 c.c. of blood in six weeks in male rats and 2.3 Gm. in female rats; with 0.05 mg. daily, the increase was from 2.9 Gm. to 4.2 Gm.; and with 0.1 mg. iron daily, the increment was from 5.5 Gm. to 6.5 Gm. The fact that the increase in our experiment was smaller than that indicated in the Smith and Otis paper can be explained by assuming either that the availability of iron from honey was lower than that from $FeCl_3$ or that actual iron content of the honeys under investigation was not as high as assumed from the data found in the literature.

SUMMARY

Laboratory rats have been fed a diet of raw whole milk supplemented with 20 per cent of honey. Rats receiving milk to which 16 per cent sucrose was added served as controls.

Rats which received a milk-dark honey mixture ad libitum showed an increase in the hemoglobin content of their blood, while the hemoglobin content of rats fed light honey or sucrose supplement in their milk gradually decreased, The gain in weight as well as the food consumption in the first group was also greater.

In paired feeding experiments, it was demonstrated that rats receiving a dark honey supplement were able to maintain their hemoglobin at almost the initial level, while the hemoglobin content of rats fed a light honey supplement declined to a level only about 30 per cent of normal, where it remained almost constant. The hemoglobin content of the blood of the control animals receiving a sucrose supplement fell steadily.

When the hemoglobin content of the blood of young rats was reduced by a whole milk diet to 6 or 4 Gm. per 100 c.c. level, the addition of 20 per cent dark honey to the milk caused a gradual increase in the hemoglobin, while the addition of 20 per cent light honey permitted a gradual further decline in the hemoglobin until a level of about 3 Gm. per 100 c.c. was reached.

It is concluded that the dark honey can play a role in the prevention and cure of nutritional anemia in rats, while light honey is less effective as a source of the blood-forming mineral elements.

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THE INFLUENCE OF DIET ON THE PHYSIOLOGIC ANEMIA OF INFANTS

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PROBLEM

THIS study is the result of a two-year experiment in a well-baby clinic to determine if the early addition of solid foods has any beneficial effect on the physiologic anemia that has been thought to occur around the sixth to ninth month in the average well baby.

It was also decided to make such a study because in the past decades the feeding of infants has undergone such tremendous changes, and also because there seem to be very few restrictions in the kind of foods used or in the time when "solids" should be introduced into a baby's diet.

PROCEDURE

The children studied were those attending the Well-Baby Clinic of the New York Infirmary. A total of 286 infants were registered for the experiment. However, due to illness or failure to attend clinics, only 177 cases were followed month by month through a twelve-month period. The duration of the study was two years. Only normal, well infants were included, and if any illness necessitated the administration of iron medication, that case was removed from the list.

Hemoglobin and red blood count estimations were made monthly. The Sahli hemoglobinometer was used for all hemoglobin determinations. The same technician did the laboratory work over the two-year period. The blood counts were taken on the day of the monthly visit, at which time each infant was carefully weighed, measured, and examined. Detailed diet changes were given in written form to each mother.

The nationalities in this group comprised the typical cosmopolitan mixture of races which one finds in a clinic in New York City. These included Greek, Irish, Negro, South American, Slav, German, and Italian, with the greatest percentage of Italian extraction.

DIETS

Three diets were used in the study.

Diet A (Advanced):

1. Strained vegetables introduced at 8 weeks of age.
2. Cereal, Egg yolk } introduced at 12 weeks of age.
3. Potatoes, meats, and fruits, after 5 months of age.
4. Breast or formula.

Diet B (Average):

1. Cereals introduced at 12 weeks of age.
2. Vegetables introduced at 16 weeks of age.
3. Potatoes, meats, and fruits, after 5 months of age.
4. Breast or formula.

Diet C (Control):

1. Breast or formula alone until 6 months of age.
2. Cereals at 6 months of age.
3. Vegetables at 7 months of age.
4. Potatoes and meats at 8 months of age.

For all infants, orange juice and some form of cod-liver oil were ordered at the first clinic visit unless there were evidences of allergy.

The infants in the advanced group who received strained vegetables at 8 weeks of age tolerated these foods well.

There were a few allergic reactions to hard-boiled egg yolk when given at 12 weeks of age, although these reactions were mild and occurred in no larger percentage than when this food is used in older children.

RESULTS

In computing the results, the average monthly hemoglobin and red blood count level of each group was estimated. There were marked individual variations in the hemoglobin level and the red blood count, but the average group ratio was found to be strikingly similar. (Figs. 1, 2, and 3.) The monthly ratios of the hemoglobin and the red blood cell count are shown in Table I. These are shown more clearly in Figs. 4 and 5.

SUMMARY

Hemoglobin and red blood cell counts begin to drop from a high level after the first two weeks of life, and the drop is persistent to the end of the eighth week. At this time many hemoglobin estimations were found to be 8 to 8.8 Gm. with red cell counts as low as 2 to 3 million. These counts are not shown in the illustrations as they are balanced by high levels obtained in other infants.

The hemoglobin begins to climb at about the eighth week, attaining an average of 10.6 Gm. around the sixteenth week.

The red blood count begins to improve between the eighth and twelfth weeks and attains a level of about 4,500,000 during the rest of the twelve-month period.

After the fourth month, there was considerable fluctuation, although no marked anemias developed between the sixth and ninth months.

The hemoglobin and red blood count levels show no demonstrable differences due to the variations in diet.

However, the babies receiving the advanced diet have at the twelfth month a very slightly higher hemoglobin concentration and red blood

TABLE I

DIET	1 TO 4 WK.	4 TO 8 WK.	8 TO 12 WK.	12 TO 16 WK.	16 TO 20 WK.	20 TO 24 WK.	24 TO 28 WK.	28 TO 32 WK.	32 TO 36 WK.	36 TO 40 WK.	40 TO 44 WK.	44 TO 48 WK.	48 TO 50 WK.
Hemoglobin													
Advanced	14.07	10.83	10.42	10.74	10.64	10.69	10.69	10.63	10.77	10.71	10.68	11.5	10.64
Average	14.02	11.21	10.49	10.52	10.75	10.88	10.92	10.75	10.93	10.84	10.75	10.68	10.55
Control	14.57	10.11	10.22	10.45	10.59	10.72	10.71	10.75	10.81	10.93	11.03	10.66	10.62
Red Blood. Cell Count													
Advanced	4,791	4,000	3,980	4,377	4,585	4,730	4,758	4,675	4,720	4,627	4,777	4,783	4,861
Average	4,780	4,083	4,036	4,270	4,566	4,684	4,619	4,681	4,626	4,742	4,779	4,705	4,852
Control	4,940	4,067	4,036	4,371	4,531	4,615	4,575	4,666	4,706	4,941	4,746	4,670	4,588

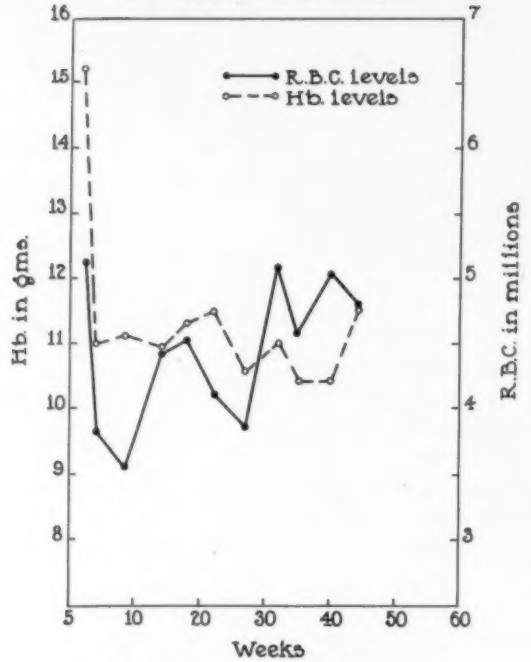

Fig. 1.—Graph of advanced diet group.

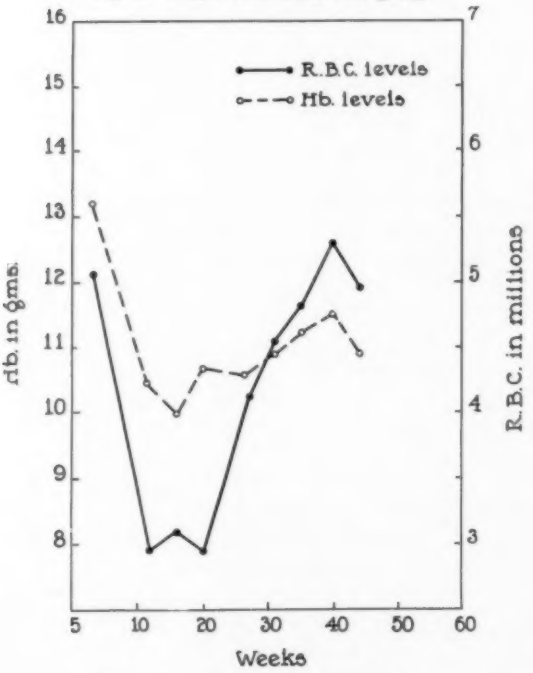

Fig. 2.—Graph of average diet group.

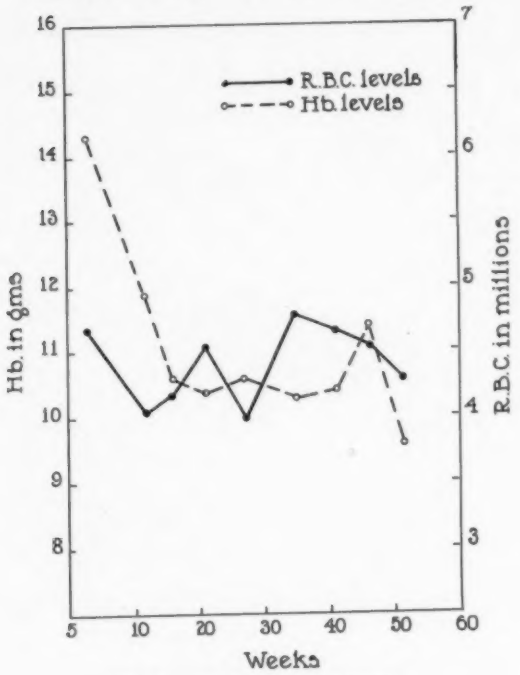

Fig. 3.—Graph of control group.

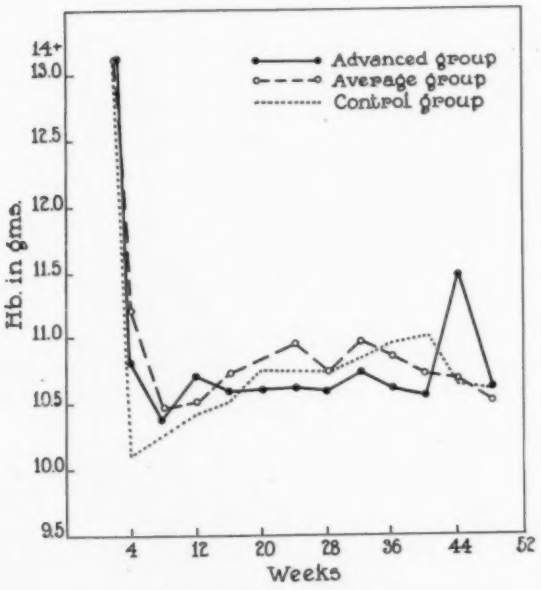

Fig. 4.—Hemoglobin study.

count. The control group shows a tendency to fall below the level of the other two groups.

During the month that solid foods were introduced, the infants in each group showed a rise in both hemoglobin and red blood count, but this elevation is not sustained.

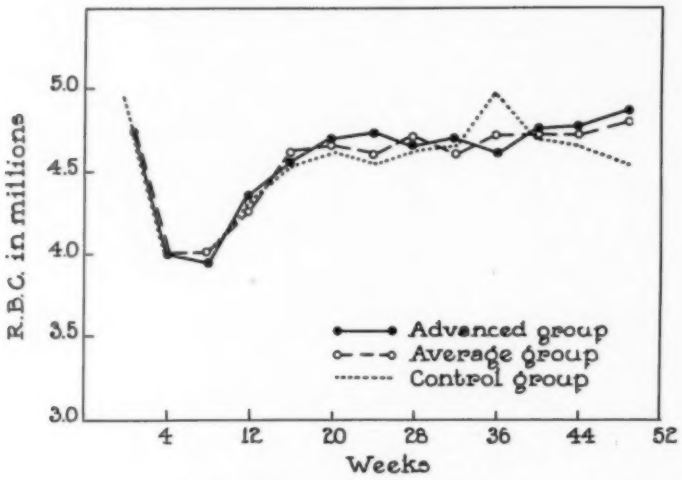

Fig. 5.—Red blood cell count study.

CONCLUSION

The early introduction of cereals, vegetables, and eggs has no marked effect on the hemoglobin level or the red blood count of infants, but nutritionally speaking, that is, in their growth (in weight and height and in their firm muscle tone) they are on the whole benefited by these dietary additions in the early months of infancy.

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THROMBOPHLEBITIS MIGRANS

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THROMBOPHLEBITIS migrans is the name applied to a type of thrombophlebitis, idopathic in origin, in which the clinical picture is sufficiently unique to justify its classification as a separate entity. This unusual disease of the circulatory system is characterized by repeated venous thromboses in isolated portions of the body, occurring simultaneously and successively with remissions and exacerbations extending over a period of months or even years. Approximately 100 cases have been recorded in adults, but to our knowledge, no cases have been previously reported in children.

It is the purpose of this paper to present a case of thrombophlebitis migrans in a 14-year-old boy, the third case recorded in which death has been proved to be due exclusively to the disease. In addition to the case report, a brief review of the literature on this subject and a discussion of the clinical, pathologic, and etiologic features of the disease will be presented.

CASE REPORT

W. K., a 14-year-old white male, was referred to the Pediatric Service of the University of Minnesota Hospital on March 18, 1940, with a diagnosis of a "possible rheumatic condition."

History.—Four months previous to admission the boy experienced moderately severe pain in the right leg and thigh, not localized, however, to the joints themselves. Simultaneously, a red, painful, indurated streak appeared along the lateral surface of the left leg. Before this subsided, pain developed in the opposite leg, and a similar streak appeared on the medial surface of that extremity. The child did not seem particularly ill, and for a time, improvement seemed to occur. Suddenly he developed severe pain in the left side of the abdomen, and a tender, red stripe appeared on the left flank. This new area of involvement had no direct connection with the previously involved areas. Following this, the right flank was affected in the same way. Sulfanilamide (exact dosage and duration unknown) was given by his physician, but no change occurred in the condition. Some time later the acute inflammation subsided, and the boy seemed better. However, edema of the right lower extremity persisted, and a network of dilated veins representing newly expanded collateral circulation became noticeable over the thighs and trunk. When he again developed a fresh area of inflammation on the anterior abdominal wall, he was referred to the University of Minnesota Hospital.

The child's past health had always been good except for rather frequent attacks of sore throat. He had had a mild sore throat shortly before the onset of the illness but not with the recurrences. There had been no varicosities, and there was no history of injury or of local infection of the parts involved. There was no tendency to disease of the cardiovascular system in the family, and the patient had had no previous disturbance of the cardiovascular system.

From the Department of Pediatrics, University of Minnesota.

Physical Examination.—The child appeared to be well developed and nourished for a boy 14 years of age and did not seem to be suffering, in spite of his four months' illness. Notable at once were the dilated, tortuous, subcutaneous veins, most marked over the thighs and trunk, which appeared to represent an expanded collateral circulation (Fig. 1). On palpation many indurated cordlike masses could be felt in

A.

B.

Fig. 1.—Infrared photographs of abdominal wall. *A*, Child with thrombophlebitis migrans, illustrating dilated and thrombosed peripheral veins. *B*, Control subject of same age.

the involved areas. These appeared to represent old, thrombosed subcutaneous veins. The freshly involved area, red, painful, and indurated, was just to the right of the umbilicus and measured about six inches in length and a little less than an inch in width. (Biopsy of this tissue was obtained later.) There was slight pitting edema of the left lower extremity and definite edema of the right leg. The circumference of the right leg measured one-quarter to three-quarter inches (0.3 to 2.0 cm.) more than the left. The head and neck, including the eyes, ears, nose, and throat, were normal except for moderately hypertrophied tonsils. The vessels of the fundi showed no pathologic changes. The heart and lungs were entirely normal; the liver and spleen were not palpable. Blood pressure was 115/70. Venous pressure in the right arm was 12 cm. and in the right ankle, 16 cm. of saline, which together with the edema, suggested involvement of the deep veins of the lower extremity.

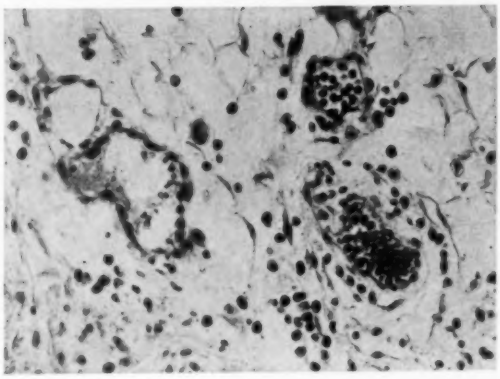
Laboratory Findings.—The hemoglobin was 73 per cent. Leucocytes varied from 6,000 to 10,000 with from 54 to 96 per cent neutrophiles. An eosinophilia of 9 per cent was found on the first count, but none was reported on three subsequent occasions. The platelet count was 135,000, and the venous clotting time was nine minutes on two occasions. Three blood cultures were sterile. Kline and Kahn tests for syphilis were negative. Agglutination tests for undulant fever and the typhoid-paratyphoid and dynsentery groups were negative. Urinalyses were uniformly negative. Throat cultures showed only *Streptococcus viridans*. The Mantoux test (0.1 mg. old tuberculin) was negative. The Schick test was positive.

Biopsy.—The biopsy specimen was taken from the area of the anterior abdominal wall which had become involved just prior to admission to the hospital. The specimen consisted of a thrombosed subcutaneous vein with adjacent inflammatory reaction. A portion of this specimen was used for culture, which was negative except for sporeformers. As there are no pathogenic aerobic sporeformers, these bacteria were considered a contaminant.

The microscopic sections (examined by Dr. E. T. Bell of the Department of Pathology and Dr. E. M. Schleicher of the Department of Hematology) revealed a fresh thrombus filling the lumen of the vein. Organization was just beginning in some portions of this thrombus, the intima showing some swelling of the cells and loss of structural detail. The media and adventitia were diffusely infiltrated with leucocytes, indicating an acute inflammatory process, which extended beyond the walls of the vein into the surrounding tissue for a short distance. Only occasional lymphocytes and neutrophiles could be seen. The vast majority of the cells were eosinophiles, which were present in the thrombus and in the perivenous tissue. More than fifty could be seen in many high-power fields, presenting a rather remarkable picture. There were a number of small vessels with many neutrophiles in the lumen but surrounded by eosinophiles which apparently had wandered through the wall, attracted somehow by the nature of the pathologic process. In places the cells lining these vessels were swollen and vague in outline, bulging into the lumen (Fig. 2).

Course of Disease.—The diagnosis of a possible thrombophlebitis migrans was made, and, in view of the widespread involvement, especially of the deeper veins, the prognosis was thought to be serious. However, no essential change occurred during the first week in the hospital. At no time was the temperature elevated, and the patient was not particularly uncomfortable. There was no indication that visceral veins had been involved in the process up to this time.

Rather abruptly, seven days after admission, the patient developed marked abdominal pain with vomiting, and the temperature rose to 101.2° F. rectally. The next morning there was moderate distention of the abdomen and some tenderness to the left of the umbilicus in an area where there was no evidence of phlebitis in the abdominal wall. Because of repeated vomiting, a roentgenologic study of the abdomen was made, which revealed gaseous distention of the small bowel. These



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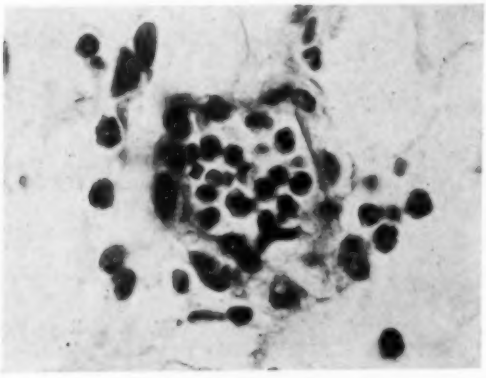

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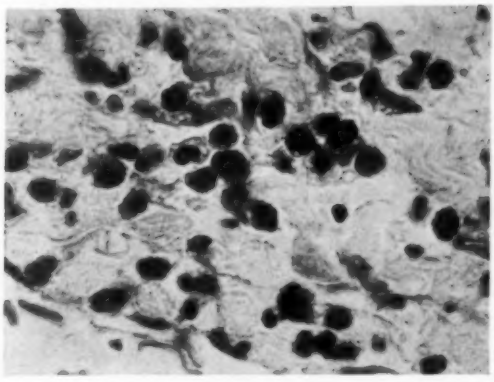

C.

Fig. 2.—Photomicrographs of a section from the biopsy specimen taken from subcutaneous tissue of the anterior abdominal wall in child with thrombophlebitis migrans.

A, Large number of leucocytes within the blood vessel and perivenous tissue. Most of the cells within the lumen of the veins are neutrophiles, while those within the surrounding tissues are almost exclusively eosinophiles.

B, Heavy filtration with eosinophiles in the wall of the thrombosed vein.

C, Swollen endothelial cells in high-power view of the vein located in the upper right portion of *A*.

findings suggested that the mesenteric veins were becoming involved. Nasoduodenal suction was instituted, and hot stupes applied to the abdomen. In addition, heparinization was attempted in an effort to prevent visceral thrombosis. A cannula was placed in the arm vein, and the patient was given 3,000 units of heparin over the ensuing twenty-four hours. By this time the abdominal symptoms had become more severe, accompanied by a rise in temperature to 103.6° F. (rectally) and leucocytosis to 21,800. The blood urea nitrogen was 49 mg. per cent; serum chlorides (as NaCl) were 641 mg. per cent, and total plasma protein was 5.9 Gm. per cent, with an albumin of 4.1 and globulin of 1.8. Definite rebound tenderness was now present to the left of the umbilicus. The patient was seen in consultation with members of the surgical and medical staffs, and it was agreed that an exploratory laparotomy be performed.

Operative Findings and Postoperative Course.—The following note of the operative findings was made by Dr. C. E. Rea: "Upon opening the abdomen, a small amount of murky, straw-colored fluid was encountered. (This proved to be sterile on culture.) There was some injection of the fatty epiploic tags of the transverse colon, and the mesenteric lymph nodes were somewhat enlarged. The bowel seemed somewhat cyanotic, but upon bringing it to the surface a normal pink color returned. The mesenteric veins were congested, but no thrombus could be found." It is, of course, possible that thrombosis had begun already in the smaller branches, but the surgeon stated that he could say with certainty that, in contrast to what subsequently was found at autopsy, there was, at least, no thrombosis of the superior or inferior mesenteric veins at this time.

Heparin was again administered and nasoduodenal suction continued. Twelve hours later the patient went into shock; blood pressure was imperceptible, and the drainage from the stomach and duodenum became sanguineous. The venous clotting time was fourteen minutes. Heparin was discontinued, and a blood transfusion was given. The systolic blood pressure rose to 95 mm. of mercury, but with slight improvement of the general condition. Treatment consisted of continuous duodenal suction, intravenous glucose and saline, and blood transfusion. He received no more heparin, and the clotting time returned to nine minutes. The duodenal drainage continued to be bloody, several tarry stools were passed, and jaundice appeared. The temperature rose to 105° F., and the patient became irrational and expired on the sixth postoperative day.

Necropsy.—The autopsy was performed by Dr. L. Berman of the Department of Pathology, and the following statements are taken from his report:

"The body was that of a fairly well developed white adolescent boy. There was generalized jaundice and slight pitting edema of the lower portion of the anterior abdominal wall. Veins of the lower extremity and over the anterior portion of the abdomen were seen prominently under the skin. Many of these were thrombosed. The superficial venous collateral circulation extended up onto the anterior surface of the thorax. There was bloody material escaping from the nares, mouth, anus, and from segments of the abdominal incision.

"The peritoneal cavity contained approximately 2 L. of unclotted dark blood. There were several old thrombi in the midportion of the abdominal vena cava. These were small, firmly attached to the wall, and did not occlude the lumen. The entire small intestine was gangrenous, and there was early gangrene of the entire colon. The splenic veins contained a soft thrombus. The hemorrhoidal veins were also thrombosed. The renal veins appeared normal.

"The spleen weighed 200 Gm. The liver was of normal size, of a uniform, yellow color, and very friable. There were no lesions of the gall bladder or bile ducts; and the pancreas, adrenals, and kidneys were normal. The axillary and retroperitoneal lymph nodes were enlarged to about twice normal size. On section they appeared free from hemorrhage, tumor, or necrosis. There was no infection of pathologic process in the abdominal cavity to which the thrombosis of the portal

system could have been secondary. The brain appeared normal; there were no thrombosed vessels and no areas of encephalomalacia. The heart and lungs showed no abnormality.''

Report on Histologic Study.—The most significant microscopic changes were in the mesenteric veins and the organs drained by the portal system. These veins were infiltrated to a varying extent with leucocytes, chiefly lymphocytes and plasma cells with occasional neutrophiles. Eosinophiles were rarely seen in these sections. The inflammation in the vein walls extended into the perivenous tissue and out into the adjacent fat. Here and there microscopic abscesses and areas of fat necrosis were present. Only in one section did a small artery contain a fresh thrombus. The walls of this artery, however, were free from inflammation and appeared normal in every respect. Elsewhere the arteries were entirely normal.

The liver showed necrosis of the central portion of its lobules, probably secondary to the portal thrombosis. In the spleen, areas of infarction were present because of venous occlusion. The kidney structure, except for some cloudy swelling of the tubular epithelium, was normal, as were all the vessels in these sections. The blood vessels of the lungs were normal; however, some pulmonary edema was noted. The heart and brain were entirely normal, as were the cardiac and intracranial vessels, except for minor toxic changes attributable to the terminal state.

The pathologic diagnosis was ''panthrombophlebitis.'' Dr. E. T. Bell, Head of the Department of Pathology, was of the opinion that thromboangiitis obliterans and periarteritis nodosa were ruled out by the pathologic findings.

REVIEW OF THE LITERATURE

Historical and Nomenclature.—The term thrombophlebitis migrans, which seems a particularly apt name for this condition, was coined in 1903 by Neisser[1] to describe a type of phlebitis which proved to be of syphilitic origin. In the first article on this subject published in America (Briggs, 1905[2]), in which three cases of the author and four collected from the earlier literature are described, the expression ''recurring thrombophlebitis of obscure origin'' is used. According to this writer, the earliest case was that reported by Jadioux[3] in 1845. The term phlebitis migrans was used by Herrick,[4] in 1911, and Hedblom in 1916.[5] Harkavy[6] (1924) and Moorhead and Abrahamson[7] (1928) applied the name ''thrombophlebitis migrans,'' which has since come into general usage. One of the most recent reviews is that of Barker,[8] who summarizes the data on forty patients with this condition seen in the Mayo Clinic.

Age Incidence.—The literature reveals that there is a notable tendency for the disease to attack young and middle-aged adults. The youngest typical case previously described, so far as we have been able to determine, was that of a 20-year-old male, reported by Jadioux.[3]. A migrating thrombophlebitis, secondary to acute infectious disease, has been reported in children by Roux[9] and Ellison.[10] Roux, in his paper entitled ''Relapsing Phlebitis,'' discusses the case of a child who suffered from attacks of thrombophlebitis following varicella at 5 years of age, complicating scarlet fever at the age of 9 years, again following an illness diagnosed as typhoid fever at 12 years and during a terminal illness at 15 years. Autopsy was not obtained in this case; however, it is quite evident that the phlebitis was a secondary complication and

not the primary type which we are discussing. Ellison, in a report entitled "Thrombophlebitis Migrans Complicating Scarlet Fever," describes the cases of two children, 6 and 10 years old, who manifested thrombophlebitis of the lower extremities, one, as a complication of the disease, the other, following recovery from the disease. He also refers to a similar case following scarlet fever reported by Huenekens and Siperstein.[11]

Clinical Features.—A compilation of the clinical features in the collected cases reveals the following facts. In the typical case the patient is not very sick, although he may be temporarily incapacitated by each attack of phlebitis. Fever of any degree is unusual, and the white blood count is usually normal, although sometimes moderately elevated. Local symptoms vary with the region involved. The usual site of onset is a superficial vein of one or the other leg. The process may then appear either simultaneously or in a series of relapses in the other leg, the arms, the subcutaneous veins of the trunk, or perhaps at another point on the same limb separated by a normal segment of vein. While it is usual for the superficial veins to be involved, they are not involved exclusively, and venous insufficiency of a limb may arise from thrombosis of the deep veins and edema may occur, followed by the development of a collateral circulation. Rarely gangrene follows such an episode. Visceral veins, too, may be involved, but how often is difficult to say because of the paucity of pathologic reports. This latter feature makes the disease dangerous, and it can be said to be the proved cause of death in three instances (including our case).

Thrombophlebitis of the mesenteric veins was said to have occurred in the cases reported by Moorhead and Abrahamson,[7] Ryle,[12] Low and Cook,[13] Krieg,[14] Hartfall and Armitage,[15] Douglas-Wilson and Miller,[16] and Stern.[17] However, this was verified by autopsy examination in only one case (Stern). Involvement of the intracranial veins was suggested in a number of case reports (Hedblom,[5] Barber,[18] Walker,[19] Kletz,[20] and Lipschitz[21]). In this series there was also only one autopsy, and in that case (Lipschitz) thrombophlebitis was found not only in the leg veins, but also in one jugular vein, with extension into the intracranial venous sinuses. The resulting infarction of the brain was the cause of death. Thrombophlebitis of the pulmonary veins has been hypothecated in a large number of cases in which symptoms suggestive of pulmonary infarction occurred. Autopsies have not been obtained in these cases, and it may be that many, if not all, were cases of pulmonary embolism from peripheral thrombi. The occurrence of cardiac symptoms in the course of this disease has led several authors to suggest that the coronary veins might sometimes be involved in the disease process (Moorhead and Abrahamson,[7] Hartfall and Armitage[15]) but there is no pathologic evidence to support this. Moreover, these cases were in an age group where disease of the coronary arteries is a real possibility.

Although the course is capricious with frequent recrudescences, recovery seems to have been the rule. When the disease reappears after a lapse of weeks, months, or years, as it may do, the involvement is likely to be at an entirely new site, although it may recur in an area previously involved. Weber and Schwarz[23] cite the case of a 49-year-old man who gave a history of repeated recurrences over a twenty-five-year period, and there are many instances of patients under observation over a period of years with a number of recurrences.

Pathology.—That information concerning thrombophlebitis migrans is meager is revealed by the fact that only two previous autopsy reports are available which can be included with certainty in this group. The first is the case of Lipschitz,[21] a 46-year-old male, in whom marked involvement of the superficial and deep veins of both legs had resulted from attacks of phlebitis and in whom involvement of the intracranial sinuses was finally the cause of death. The second is the case of Stern,[17] a 60-year-old woman who died of a mesenteric venous thrombosis after having had many attacks of thrombophlebitis involving all four extremities, the trunk, scalp, and neck. At autopsy there was an extensive thrombosis of the mesenteric veins with gangrene of the bowel. They were unable to find the point of attachment of this thrombus, and the sections studied microscopically showed no inflammation of the vein wall but did show some thickening of the endothelium. In both of these cases the autopsy findings were consistent with the diagnosis of thrombophlebitis migrans. Stern reports a second case, but this patient, who suffered a series of attacks of thrombophlebitis during her last three months of life, proved to have a carcinoma of the liver and so cannot be included in this series. Similar objections apply to the case of Keibl and Köberle[24] and to that of Hirschhorn, Lisa, and Goldstein,[22] in that both these subjects had severe heart disease with cardiac decompensation as well as other complications.

Although the clinical features of thrombophlebitis migrans are distinctly different from those of a secondary thrombophlebitis, the histologic appearance of the two types is similar. Microscopic sections of a considerable number of veins removed during different phases of the disease process have shown acute or chronic inflammatory changes, usually of all the coats of the vein wall, depending upon at which stage the biopsy was taken. As a rule, but not always, there was a thrombus in various stages of organization filling the lumen. There are some reports in which the lumen was occluded by a thrombus without any inflammation of the adjacent vein wall. Such sections were thought possibly to have been taken through a thrombus that had grown considerably beyond its site of attachment and do not necessarily indicate, therefore, that phlebitis was not present. Barker[5] found the vein wall heavily infiltrated with connective tissue which sometimes contained giant cells. This pathologic picture he considers essentially indistinguishable from that seen in the veins in cases of thromboangiitis

obliterans, a similarity previously pointed out by Buerger[25] and Harkavy.[6] None of the published reports contain any mention of the finding of eosinophiles in significant numbers, as were noted in the biopsy obtained from our patient (Fig. 2).

Etiology.—The etiology of thrombophlebitis migrans remains obscure, although a number of causes have been suggested. Blood studies made to determine whether or not a disturbance in the clotting mechanism itself is at fault have shown that no such abnormality exists. A number of investigators have suggested that a congenital vulnerability of the veins of these patients may be responsible for the disease, but no familial trends are discernible in the collected cases. Attempts to culture bacteria from the blood stream during the acute phase of the disease have proved to be almost uniformly futile, although Walker[19] reported finding *B. alkaligenes* and Hedblom[5] "nonmotile sporeformers" in the blood stream. Gougerot and Frumusan[26] found gram-positive encapsulated diplococci in a biopsy specimen; however, cultures from the same specimen proved to be sterile. Stern[17] and Barker,[8] using both aerobic and anaerobic culture techniques, failed to grow any organisms from fresh biopsy specimens. Not only has the possibility of septicemia and bacteremia been considered, but also the question of focal infection. The latter aspect has been emphasized by a large number of authors, and there are a number of patients who were considered to be cured following the removal of such foci. Krieg[14] suggests that an allergic type of sensitivity may play a role in the pathogenesis of this condition. He theorizes that there develops in the venous tissues a local sensitivity to the bacterial products of a distant focal infection.

The possible fundamental relationship between thrombophlebitis migrans and thromboangiitis obliterans (Buerger's disease), the etiology of neither of which is known, has been mentioned, and Buerger himself is inclined to believe that they are the same disease. Thrombophlebitis of the superficial veins is the first symptom of Buerger's disease in a certain percentage of cases. d'Abreu[27] reports the case of a man who had episodes of unexplained thrombophlebitis at the ages of 12, 43, 46, and 50, and who died at the age of 52 years with gangrene and a typical picture of thromboangiitis obliterans proved at autopsy. Barker points out that in many cases of thromboangiitis obliterans only the arteries are involved; in others, that the involvement encompasses both veins and arteries. He suggests that thrombophlebitis migrans might conceivably be a form of thromboangiitis obliterans in which veins alone are involved, and his pathologic studies tend to support this view.

Treatment.—A variety of therapeutic measures have been suggested by different writers; however, none have been shown to be of much actual value. It appears that each individual attack should be treated in the manner of any ordinary local thrombophlebitis, with the aim of relieving venous insufficiency and preventing embolism. The usual mode of attack has been to eliminate suspected foci of infection, and a number

of recoveries have been reported coincident with this procedure.[15, 20] Nothing has been suggested, however, that will prevent recurrences at some future time.

COMMENTS

The mechanism of thrombosis formation in arterial vessels is quite well understood and almost invariably is initiated by degenerative changes in the vessel wall. In striking contrast to this, the method of production of venous thrombosis is far from clear. Even the question of whether the inflammation in the wall of the thrombosed vein is the cause or the result of the thrombus is still unsettled. In general, a number of factors are known to contribute to or predispose the development of venous thrombi. Stasis that results from prolonged recumbency, varicosities, cardiac failure, pregnancy, or local venous compression plays an undoubted role in the production of certain thrombi. Infectious disease by means of toxemia, dehydration, and sometimes by direct bacterial assault is responsible for others. Mechanical, chemical, or thermal trauma to the vein wall or involvement by a contiguous inflammatory process are obvious causes, if present. The slow-moving, viscid blood of polycythemia vera and certain cases of congenital heart disease also can be responsible for thrombus formation. In the majority of cases of thrombophlebitis some such factor actually is demonstrable. However, as Barker says, "A certain type of thrombophlebitis occurs as a primary disease. It affects robust, healthy individuals who have not recently undergone operation or had infectious disease; it occurs without relation to childbirth, injury, or local infectious process, and it may occur in the absence of cardiac decompensation, blood dyscrasia, severe constitutional disease, or previous or associated disease of the vein." This primary nature is the first characteristic which distinguishes thrombophlebitis migrans. The second is its migratory character.

Buerger as well as Barker and Harkavy believe that this disease is identical with, or at least one phase of, thromboangiitis obliterans. It is not inconceivable that certain cases may be related to other known types of thrombophlebitis. Our findings, however, as well as those of the majority of others reported in the literature, appear rather to support the concept of its primary nature.

There appears to be no evidence that such factors as fundamental deficiencies in the clotting mechanism or congenital vulnerability of the veins are significant in the production of this condition.

The theory of infectious etiology cannot be overlooked, yet it does not seem likely that actual bacterial invasion of the vein wall takes place. The inability of numerous investigators, including ourselves, to demonstrate organisms in the blood stream or on culture of fresh tissue speaks against a bacterial agent as being the cause. However, the possibility of invasion by a virus has not been ruled out. Krieg's concept that damage to the venous tissue may result from contact with the products of a distant bacterial infection to which the body has become sensitized is a

possibility. There seems to be no reason to limit the possible allergin to a bacterial product, as any foreign protein might be responsible for such a phenomenon.

The eosinophilic inflammation in the biopsy specimen from our subject suggests the possibility of a related allergic reaction. The ultimate explanation of local eosinophilia is unknown, but its frequent association with allergic processes is well recognized. The initial blood eosinophilia tends further to bear out this possibility. The subsequent disappearance of circulating eosinophiles is not necessarily inconsistent, as it has been shown experimentally that coincident with the development of local eosinophilia there may occur a disappearance of these cells from the blood until the bone marrow has had an opportunity to replace them.[28] Moreover, the concept of allergic damage to vascular tissue is not altogether new. It has been expressed in rheumatic fever, periarteritis nodosa being called an allergic manifestation.[29] Among the changes found when a foreign serum is injected into a sensitized rabbit is damage to the endothelial lining of small vessels.[30] The widespread swelling and loss of cellular detail in the endothelium in our histologic specimen demands some explanation, as does the intense eosinophilic inflammation that was present.

Two of the newer therapeutic agents, heparin and sulfanilamide, proved disappointing in the treatment of our patient. Such encouraging results had been reported from the use of heparin in the secondary types of thrombophlebitis that a trial in this patient seemed justified, especially when it appeared that mesenteric thrombosis was developing. Instead of being benefited, the patient developed shock and intestinal bleeding. Autopsy findings indicated that these symptoms were probably due to the extensive mesenteric thromboses and not to the heparin. If this be true, a comparison of the findings at operation and at autopsy indicates that mesenteric thrombosis occurred or at least vastly extended itself in the presence of what appeared to be satisfactory heparinization. From this experience, we are forced to believe that the usefulness of heparin in this type of thrombophlebitis is definitely limited. It could not be ascertained exactly how much sulfanilamide the patient had received before entrance to the hospital. An adequate trial with one of the newer sulfonamides was being contemplated when the onset of mesenteric thrombosis rapidly put an end to our opportunity to study the condition. Such a trial, however, seems justified in the event of further experience with such a case. Removal of the foci of infection, if present, should also be instituted as a therapeutic procedure; and, in the light of the findings of our case, it would not seem unreasonable to search for an allergic offender. There was no opportunity to determine the effect of regional block of the sympathetics, but Ochsner[31, 32] reported encouraging results following this procedure in the secondary type of thrombophlebitis. Although it is possible that our patient represents an anachronous appearance in a child of what is typically a disease of

adults, it seems more likely that wider interest in the condition will bring to light additional patients in the pediatric age group.

CONCLUSIONS

Thrombophlebitis migrans, a rare clinical syndrome characterized by repeated venous thromboses occuring intermittently or concurrently, chiefly in the superficial veins in various parts of the body and of obscure origin, is described for the first time in a child. Heparinization proved to be unsuccessful in preventing further venous thrombus formation. Autopsy studies (third performed in this condition) showed death to be due to the development of mesenteric thrombosis. Bacteriologic studies gave no clues to the underlying etiology. However, the histologic findings of eosinophilic inflammation and swelling of the intima of an involved vein suggested that some sort of allergic phenomenon may be associated with the production of the clinical picture.

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STUDY OF THE BIRTH WEIGHTS AND PONDERAL GROWTH OF CHILDREN OF TUBERCULOUS MOTHERS

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PROFESSOR Alejandro Raimondi, in 1938, presented to the National Medical Academy statistics (in which one of us [C. A. U.] had collaborated) on the birth weight of children of tuberculous mothers. These statistics were obtained from children born in the Maternity Ward of the Tornu Hospital from its foundation in 1925 to March, 1938. (Stillborn children were not included.) These coincided approximately with the statistics given in 1925 by Debré and Lelong[1] on 433 cases, and those given by Couvelaire and Lacomme[2] on 500 cases, all of them being newborn children of tuberculous mothers.

Since then (1938), 240 more children have been born in the Maternity Ward of the Tornu Hospital. In Table I we have, in the second column, the figures presented in 1938; in the third, those corresponding to the 240 new cases; and in the fourth, the total; that is, 1,373 children of tuberculous mothers born in the Tornu Hospital up to August, 1940.

The 1,373 patients were divided into two groups: (1) those whose mothers were seriously ill; and (2) those whose mothers were slightly affected. In the first group were included those who presented obvious signs of activity and died when lying-in, and those who, when discharged after delivery, were in a state worse than or similar to that in which they entered the hospital. The second group included all the others; that is, those who had little or no signs of activity and were discharged as improved as far as their tuberculosis was concerned. The fact that the meticulous medical examination of consumptive mothers was carefully done in every case by Dr. A. A. Raimondi, Director of the Municipal Antituberculosis Campaign, gives more value to the diagnoses upon which we based our statistics.

A comparison of Column 2 with Column 4 shows a striking similarity between the slightly ill and the healthy women.

One notes from Table II and Fig. 1 that only among tuberculous mothers in whom the disease is far advanced and whose metabolism is generally disturbed are the babies extremely small. It would appear, then, that maternal tuberculosis in itself, as an infection, does not predispose to premature or underweight children.

PONDERAL GROWTH DURING INFANCY OF THE CHILDREN OF TUBERCULOUS MOTHERS

In the report by Raimondi and Urquijo,[3] it was stated that children of tuberculous mothers, weighing more than 2.5 kg. at birth,

TABLE I

BIRTH WEIGHT (KG.)	1925-1938	1938-1940	TOTAL
Less than 1.5	31	15	46
Between 1.5 and 2.0	76	6	82
Between 2.0 and 2.5	121	31	152
Between 2.5 and 3.0	211	46	257
Between 3.0 and 3.5	348	90	438
Between 3.5 and 4.0	243	32	275
Between 4.0 and 4.5	92	19	111
More than 4.5	11	1	12
Total	1,133	240	1,373

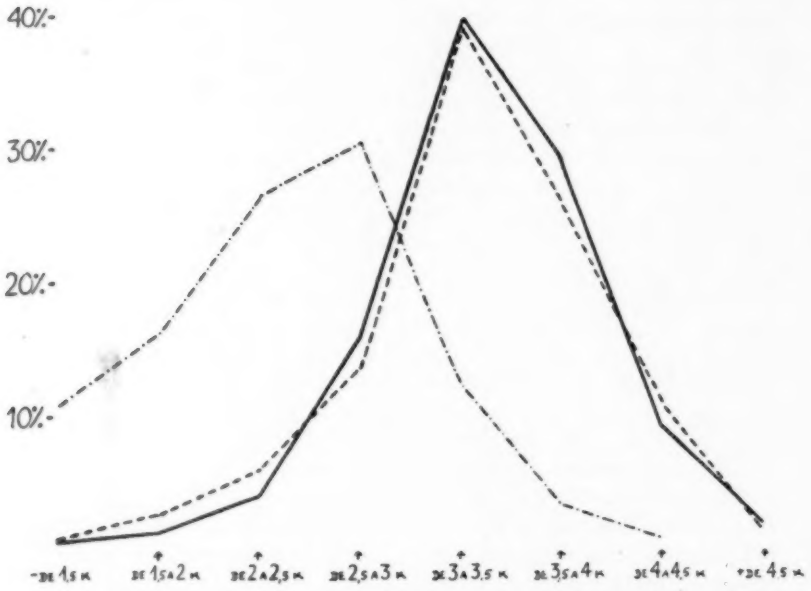

Fig. 1.—Birth weights of infants of tuberculous and healthy mothers. Infants of mothers with far advanced tuberculosis, - - . - . - ; infants of mothers with minimal tuberculosis, ——— ; infants of healthy mothers, ————.

TABLE II

WEIGHTS OF CHILDREN BORN OF TUBERCULOUS AND NONTUBERCULOUS WOMEN

BIRTH WEIGHT (KG.)	SERIOUSLY ILL	SLIGHTLY ILL	HEALTHY* (%)
Less than 1.5	38 (10.79%)	8 (0.78%)	0.62
Between 1.5 and 2.0	57 (16.19%)	25 (2.44%)	1.19
Between 2.0 and 2.5	93 (26.42%)	59 (5.77%)	3.96
Between 2.5 and 3.0	107 (30.31%)	150 (14.76%)	15.52
Between 3.0 and 3.5	43 (12.21%)	395 (38.63%)	39.36
Between 3.5 and 4.0	11 (3.12%)	264 (25.80%)	28.90
Between 4.0 and 4.5	3 (0.86%)	108 (10.55%)	8.91
More than 4.5	–	12 (1.27%)	1.53

*Based on study made by Professor Pedro Escudero on 10,297 deliveries of nontuberculous mothers, *The Weight and Height of the Newborn Baby*, Buenos Aires, 1940, National Institute of Nutrition, No. 11.

develop similarly to children of similar weight born of healthy mothers. The same is true for infants weighing 2.5 kg. or less.

These data, established on the 531 children put in Family Placement between 1931 and 1938, have been confirmed in this study of 164 children who have also been placed since 1938.

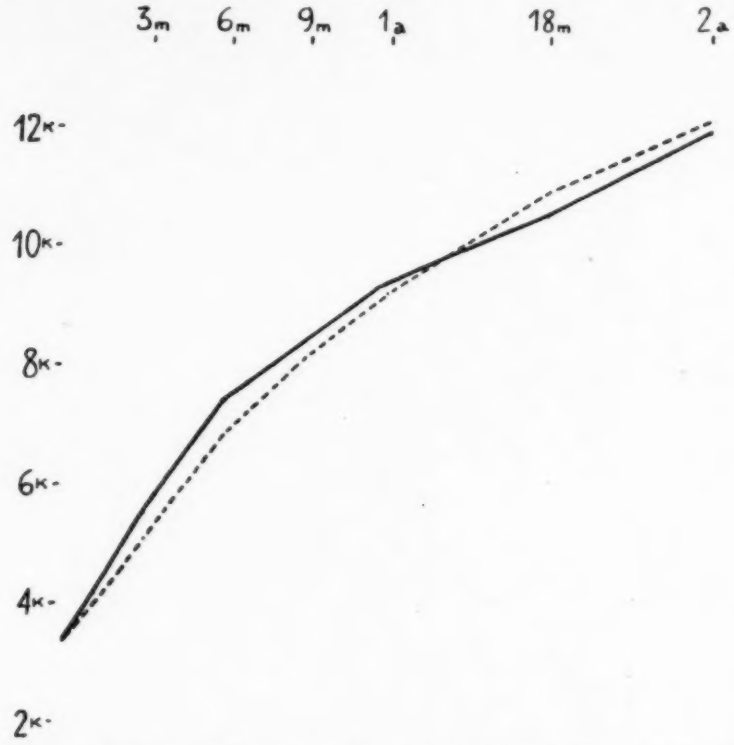

Fig. 2.—Ponderal growth of infants weighing more than 2,500 Gm. Infants of tuberculous mothers, - - - - - - - - ; infants of healthy mothers, ————.

In Table III the second column represents children weighing more than 2,500 Gm. at birth who were born to tuberculous mothers; the third represents the new figures; and the fourth represents the totals. In the last column the normal weight of children of the same age is shown. The figures in parentheses indicate the number of cases upon which we have established our statistics.

In Table IV and Fig. 3 are listed the children in whom the birth weight was less than 2,500 Gm., who were born to tuberculous mothers. Here again are given the figures for the various years studied as well as normal values. The normal values are based on a study of twenty-nine children whose birth weight was less than 2,500 Gm. who were followed for one year by one of our dispensaries directed by Dr. P. R. Cervini.

TABLE III

AGE IN MONTHS	1931-1938	1938-1940	TOTALS	NORMAL FIGURES
3	5,062 (400)	5,209 (139)	5,099 (539)	5,500 (405)
6	6,793 (344)	6,928 (127)	6,831 (471)	7,400 (363)
9	8,136 (321)	8,252 (114)	8,186 (435)	8,450 (269)
12	9,186 (295)	9,415 (108)	9,247 (403)	9,400 (259)
18	10,958 (155)	10,763 (88)	10,909 (243)	10,550 (151)
24	12,181 (209)	12,095 (72)	12,158 (261)	11,950 (99)

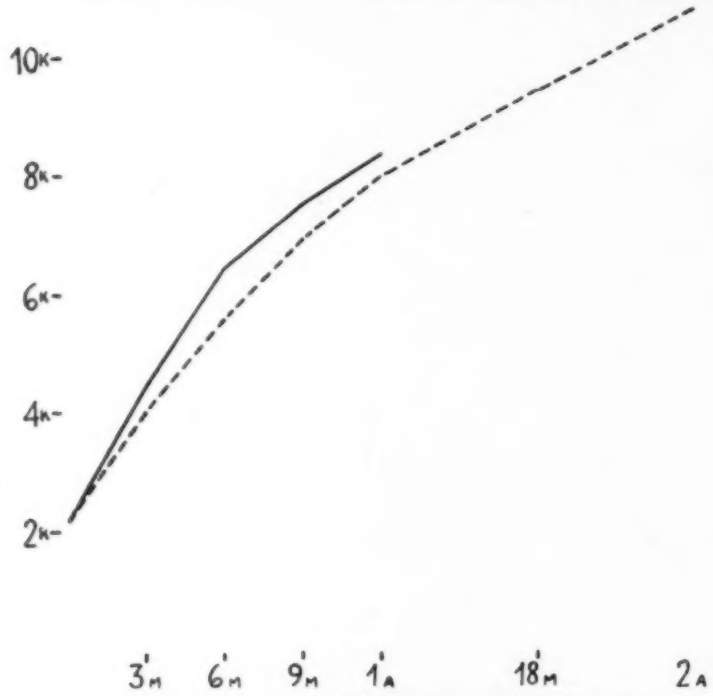

Fig. 3.—Ponderal growth of infants weighing less than 2,500 Gm. Infants of tuberculous mothers, ---------; infants of healthy mothers, ————.

TABLE IV

CHILDREN WEIGHING LESS THAN 2,500 GM. AT BIRTH WHO WERE BORN TO TUBERCULOUS WOMEN

WEIGHT (GM.)	1931-1938	1938-1940	TOTALS	NORMAL FIGURES
At birth	2,175 (80)	2,090 (23)	2,165 (103)	2,179
At 3 months	4,013 (72)	3,967 (18)	4,004 (90)	4,439
At 6 months	5,666 (63)	5,358 (17)	5,588 (80)	6,450
At 9 months	6,890 (56)	6,844 (15)	6,880 (71)	7,450
At 12 months	7,910 (48)	8,015 (16)	7,838 (64)	8,326
At 18 months	9,370 (39)	9,374 (13)	9,371 (52)	
At 24 months	10,650 (33)	10,912 (10)	10,710 (43)	

In medical literature, we have found only two statistics similar to ours: the one by Lelong[4] in 1924 on forty-six children of tuberculous mothers, and the one by Heinemann and Malmberg[5] in 1935 on twenty-nine cases (Fig. 3).

TABLE V

BIRTH WEIGHT (GM.)	WT. LESS THAN NORMAL	WT. HIGHER THAN NORMAL
Less than 2,500	7 (70.0%)	3 (30.0%)
From 2,500 to 3,000	10 (58.8%)	7 (41.9%)
From 3,000 to 3,500	12 (30.7%)	27 (69.3%)
More than 3,500	3 (12.0%)	22 (88.0%)

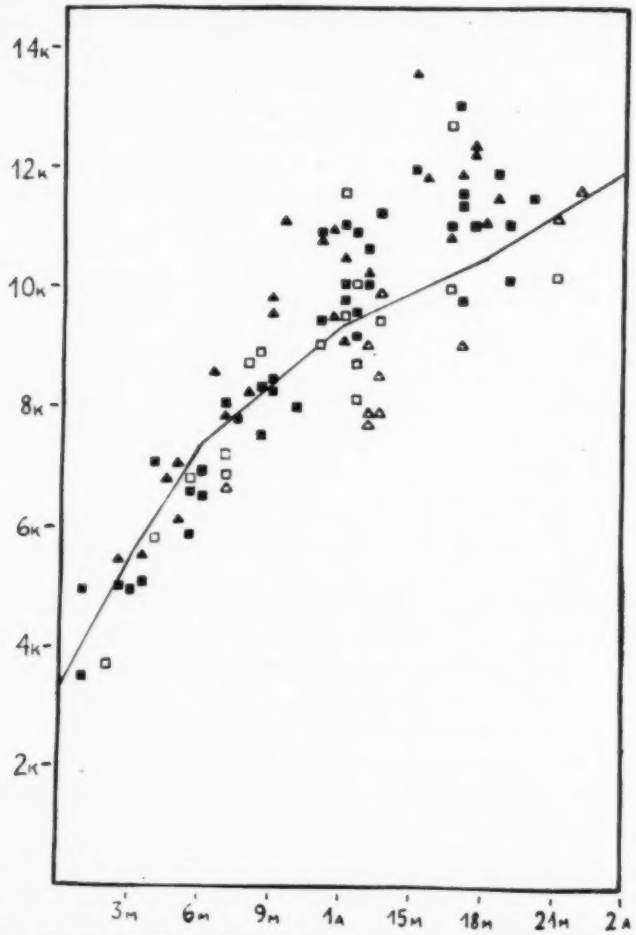

Fig. 4.—Weights of children between ages of 1 month and 2 years born of tuberculous mothers. △ Birth weight less than 2,500 Gm. □ Birth weight between 2,500 and 3,000 Gm. ■ Birth weight between 3,000 and 3,500 Gm. ▲ Birth weight greater than 3,500 Gm.

From the studies thus far presented, one may infer that newborn infants of tuberculous mothers, separated at birth but obtaining adequate care and proper diet, will gain weight to the same degree as children born of healthy mothers and similarly cared for. In the premature or underweight infants, there may be a lag in weight gain at the onset. This may be due, in part, to the separation from the mother, and also to a nonspecific lowering of vital capacity (Sayé) seen in infants born of mothers suffering from any wasting disease.

Fig. 4 depicts the actual weight curves of infants born of tuberculous mothers and sent to Family Placements, healthy foster mothers who generally had a family of their own. This figure includes children from 1 month to 2 years of age. Thirty-two of the children have weights considered below normal, while sixty-one are comparable to or slightly above the norm. In Table V the distribution of these children with reference to their birth weights is given.

It is clear from this table that birth weight greatly influences subsequent development; however, it is not uncommon to see underweight children overcome their original deficit and surpass those of normal birth weights.

CONCLUSIONS

1. Serious maternal tuberculosis is sufficient cause for premature delivery.

2. The birth weight of a child born of a tuberculous mother, not seriously ill, is similar to that of a child born of a healthy mother.

3. Tuberculosis, considered as to infection, does not cause delivery of a small fetus; prematureness of the child of a seriously ill tuberculous mother must be accounted for by the great deficit in the general condition of the mother and not by the tuberculous infection.

4. The ponderal growth of a child born with normal weight to a tuberculous mother is similar to that of a child born with normal weight to a healthy mother.

5. The ponderal growth of a child weighing less than 2,500 Gm. at birth, who was born to a tuberculous mother, is similar, although slightly inferior, to that of a child of equal weight born to a nontuberculous mother.

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LAURENCE-MOON-BIEDL SYNDROME

A Report of Two Cases with Unusual Combinations of Heredofamilial Deviations

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ABOUT 150 cases of the Laurence-Moon-Biedl syndrome have been reported since it was first described by Laurence and Moon in 1866.[1] This small number of recorded cases might suggest, on the one hand, that the disease occurs rarely, or, on the other hand, it might indicate that some confusion still exists concerning the different symptoms which form this disease. It was originally thought that the disease constituted a syndrome characterized by the following symptoms: obesity, hypogenitalism, retinitis pigmentosa, mental deficiency, poly- or syndactylism, and familial occurrence. A review of the literature reveals that this assumption does not hold true, because as Warkany, Frauenberger and Mitchell[2] have shown, in the great majority of the cases "this syndrome does not represent a disease entity but it is a rare combination of more or less frequent heredofamilial symptoms." They substantiated this statement by an analysis of the cases published up to 1937 which showed that out of 102 patients reported as manifesting this syndrome, only twenty-four showed the combination of all the characteristic symptoms mentioned above. The remaining seventy-eight patients did not present all of the required symptoms. Among the seventy-eight incomplete cases, there were wide variations in the type of symptoms present. Symptoms such as dwarfism, atrophy of the optic nerve without retinitis pigmentosa, strabismus, nystagmus, deafness, congenital heart disease, atresia ani and deformities of the skull were listed as of equal importance with the basic sextet of symptoms thought to be pathognomonic of this syndrome.

Laurence and Moon in their monograph[1] spoke merely of "retinitis pigmentosa accompanied by general imperfection of development," while Biedl[3] suggested that the disease represents a syndrome of deformities in which obesity forms one of the striking items, and furthermore that the obesity might be accompanied by one or more congenital deformities. He considered retinitis pigmentosa to be one of the accompanying congenital deformities and its presence not essential to the diagnosis. It might be replaced by anyone of the other aforementioned congenital defects.

Warkany and associates[2] in their study came to the conclusion that "the designation as a syndrome of the five hereditary symptoms,

From the Child Guidance Home of the Jewish Hospital.

retinitis pigmentosa, obesity, hypogenitalism, mental retardation and polydactylism, has been shown to be unjustified." They contend that the so-called Laurence-Moon-Biedl syndrome is only one of many forms of heredofamilial deviations in which many different combinations of symptoms are possible, and that therefore "the construction of syndromes, which is in most cases an arbitrary procedure, tends to obscure rather than to reveal the true picture." The same authors suggested, moreover, that "it would be of great value to know which combinations of hereditary deviations are found together frequently and which are rarely associated."

For this reason, the following cases are reported. In addition, they also present a combination of symptoms which have never before been recorded in the literature.

REPORT OF CASES

CASE 1.—E., a white boy aged 13½ years, was referred to Child Guidance Home by the Vocational Counselor of his school because of his poor school achievement and also to determine what role his hearing defect was playing in the problem. His impaired hearing had been noted since early infancy.

Family History.—There was no blood relationship between the parents. Nothing unusual was found on the paternal side of the family. There was no history of epilepsy, mental or nervous disease, alcoholism, glandular disturbances, polydactylism or syndactylism, or other congenital defects. The father himself was in good health and of a pleasant and outgoing personality. The mother also was in good health and on examination showed no physical defects except for the presence of syndactylism in both feet. One maternal niece was said to have one "very large" toe and was seen for this condition by several physicians, who, according to patient's mother, were unable to account for the condition. One maternal uncle and one maternal aunt became blind very early in life, but the informant was not able to give further details about this point.

The patient had three sisters and two brothers, all older than he, and apparently all were in good health and none of them ever presented symptoms similar to those seen in patient.

Past History.—The patient was born to a multipara aged 34. His birth and delivery were uneventful and his infancy was not remarkable. Dentition began at the age of 5 or 6 months; he walked at about one year of age and talked at one and-half years of age. When he was about 7 months of age, he suffered from a convulsion, but his mother believed that this convulsion followed a hurried breast feeding. Nutrition, sleep, and excretory habits were normal. The only childhood disease the patient experienced was measles at the age of 5 years. Except for this and the hearing defect, which was discovered very early in infancy, the boy was never ill.

Present Complaint.—At the time of admission, the patient's difficulties consisted merely of poor school achievement which the counselor of the school thought might be partly due to the boy's impaired hearing. The mother, however, stated that the boy was never considered a bright child and always had difficulty with his work in school. In spite of this, except for a repetition of the second grade, he always managed to be promoted, although his marks were always just passing. The boy never presented any behavior problem either at school or at home.

Physical Examination.—The positive findings on general physical examination were syndactylism in both feet, marked obesity, small and undeveloped genitalia, large cryptic tonsils, and slightly reddened throat. The blood pressure was 110/74.

Visual Examination.—The ophthalmologist reported as follows: Vision, R. 8/15; L. 8/10. The fundi were normal. The discs showed no atrophy and no diminution in the caliber of the blood vessels. No retinal pigment deposits were seen.

Ear Examination.—The drums were normal. Bone and air conduction were decreased on the left and slightly decreased on the right. On the audiometric test a hearing loss of 24 per cent in the right ear and of 40 per cent in the left ear was noted. A diagnosis of nerve-type deafness was made by the otologist.

Neurologic Examination.—The facial expression was blank and rigid. There was facial asymmetry, jerking movements of the head, and ptosis (slight) of both eyelids. The pupils were slightly irregular but otherwise negative. The Romberg sign was positive, there was some unsteadiness in the gait, and a tremor of the outstretched hands was present. The tongue deviated to the right with marked tremor. The biceps, triceps, and wrist reflexes were hypoactive on both sides. The patellar and Achilles tendon reflexes were hypoactive on the right side and normally active on the left side. There was no ankle or patellar clonus. All the plantar reversals were negative, and the superficial reflexes were normal. There was no disturbance of sensation.

Endocrine Examination.—The patient was three and one-fourth inches underheight for his chronologic age and twenty-four pounds overweight for his height (nine pounds overweight for his chronologic age). He had the female type of skeletal development with broad pelvis and knock-knees. The fingers were short, broad, and spaded. No hyperextensibility was present. The fat distribution was principally of the mons-mammary-girdle type. A slight amount of nuchal fat was also present. Both testes were descended, but the genitals were very small and no secondary sex characteristics were present.

X-Ray Findings.—Skull: negative, no deformities. Sella turcica: normal. Paranasal sinuses: antra clear. Chest: heart and lungs normal. Bone development: Bone age, 10 years; no skeletal deformities; syndactylism as well as abnormally large bones were seen in both feet.

Laboratory Data.—Repeated blood counts and urinalyses were all within normal limits. Blood serology was negative. The tuberculin test was negative. The blood chemistry revealed cholesterol, 149 mg.; calcium, 11.3 mg.; phosphorus, 5.8 mg.; and the nonprotein nitrogen, 36.1 mg. The androgen test revealed 14 mg. of 17 ketosteroid. The basal metabolic rate was plus 9 per cent. The glucose tolerance test gave the following values: fasting sugar, 108 mg.; first hour specimen, 114 mg.; second hour specimen, 108 mg.; third hour specimen, 103 mg. The corresponding urine specimens were all negative for sugar and acetone.

The Mosenthal test for kidney function gave the following results:

SPECIMEN	VOLUME (C.C.)	SPECIFIC GRAVITY
8 to 10 A.M.	75	1,024
10 A.M. to Noon	60	1,023
12 to 2 P.M.	95	1,020
2 to 4 P.M.	105	1,018
4 to 6 P.M.	70	1,024
6 to 8 P.M.	120	1,020
8 P.M. to 8 A.M.	455	1,022

(Total day volume, 525 c.c.; Total night volume, 455 c.c.)

Electrocardiogram.—This revealed a normal record with sinus rhythm. Rate, ninety-three per minute.

Electroencephalographic Findings.—The examiner reported as follows: "A six-lead monopolar study was done. The record is good technically. There is a moderate amount of 10½ to 11 per second rhythm throughout the record. There is also the usual amount of faster activity which is probably normal beta rhythm. However, there is a great deal of activity of around 4, 5, and 6 per second of rather high voltage. This is most marked in the parietal and frontal areas, although

there is some in the occipital leads as well. Hyperventilation slows the record moderately and brings out the abnormalities already mentioned. There are no localized abnormalities.

"Impression: This is a grossly abnormal record. The record is consistent with rather severe cerebral dysrhythmia with no definite classification nor localization." (Fig. 1.)

Psychometric Examination.—On the new Stanford-Binet test, Form M, the boy had an I.Q. of 79. The results of the Stanford Achievement test corresponded with his mental age level.

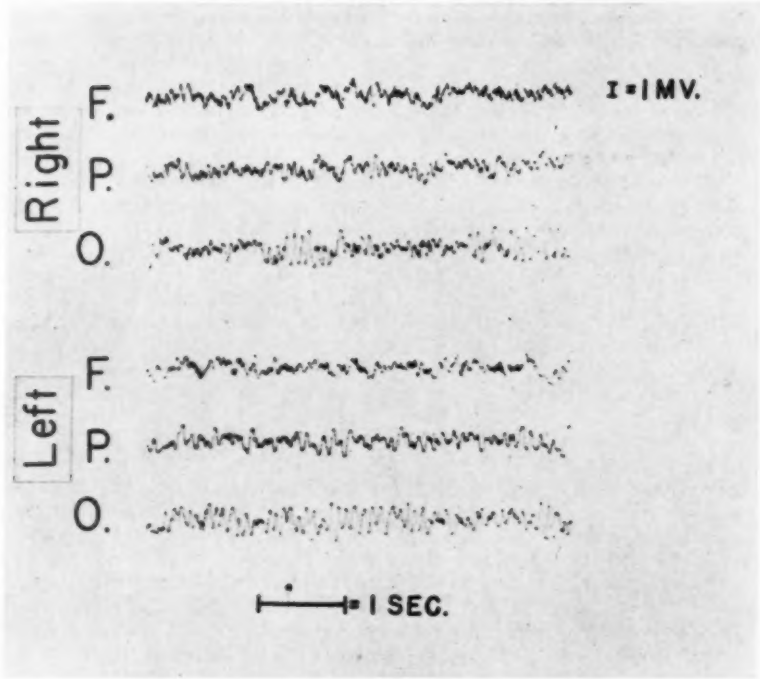

Fig. 1 (Case 1).—Electroencephalogram showing increased activity of four, five, and six per second waves of high voltage.

Social Maturity Test.—On the Vineland social maturity scale, the boy obtained a S.Q.* of 98.3.

Psychiatric Examination.—This did not reveal anything of importance. The boy's impaired hearing was obvious. There was some blankness of facial expression present. Head jerking could be observed. During conversations, the boy gave the impression of being rather dull. His emotional responses were somewhat superficial; however, he seemed to have insight into his problems. A slight speech defect was also noted. He was very ill at ease, fearful, and a feeling of inferiority and insecurity was apparent.

Course at Child Guidance Home.—The boy adjusted somewhat slowly to the general routine but presented no problem whatsoever. He mixed well with the group and was well liked by the other children. The boy appeared to be somewhat fearful

*S.Q., social quotient.

and timid in the presence of adults. He was a good eater, but his appetite was not enormous nor did he drink excessively. No enuresis occurred. It was noted that his attention span was short and that he had no special interests. His only interest was in playing pool, and he spent most of his spare time in this activity. Jerking of his head was noted; his coordination was good, however.

CASE 2.—M., a 20-year-old white girl, was referred because she had no ambition and no desire to work. She spent most of her time listening to the radio. According to the mother, the girl is intellectually retarded and has many nervous mannerisms. This condition has existed for many years.

Family History.—There was no blood relationship between the parents. The paternal grandfather and one paternal uncle were feebleminded. Both the paternal grandfather and father have syndactylisms in both feet. Otherwise the family history is entirely negative.

Past History.—The patient was born to a multipara after a normal pregnancy. Birth and delivery were uneventful. Her infancy was not remarkable. Dentition began at the age of 8 months, but walking was delayed. Patient started to walk at about 2 years of age. No definite information could be obtained concerning talking but mother thinks this was within normal limits. Nutrition, sleep, and excretory habits were normal. Patient had pertussis and diphtheria in early childhood and at the age of 2 years, her eyes became crossed. Patient started to menstruate at the age of 17. Periods are irregular and flow is scanty, lasting but one day. Patient also suffers from dysmenorrhea. Patient has a huge appetite and is especially fond of sweets. She also drinks a great deal of water.

Present Illness.—Present illness dates to the time patient started to school. The girl did very poor work in school and failed many times. Since stopping school, the girl has never worked, always sitting around the house doing nothing. Mother thinks that the girl's hearing is impaired because she does not understand simple directions.

Physical Examination.—The general physical examination was negative except for syndactylism in both feet and marked obesity. The blood pressure was 136/90.

Visual Examination.—The ophthalmologist reported as follows: Vision normal. Retinal findings are not characteristic of retinitis pigmentosa, although the periphery shows disturbances in the retinal pigment epithelium, which is suggestive of tapioretinal degeneration.

Ear Examination.—The drums were normal. Both bone and air conduction were slightly decreased on the left and markedly decreased on the right. On the audiometer a hearing loss of 24 per cent was noted in both ears. A diagnosis of nerve type deafness was made.

Neurologic Examination.—This was entirely negative except for internal strabismus of the right eye.

Endocrine Examination.—The patient was three and three-fourths inches underheight for her chronologic age and forty-seven pounds overweight for her height (thirty-six pounds overweight for her chronologic age). She had the female type of skeletal development with broad pelvis and knock knees. The fingers were short, broad, and spaded. No hyperextensibility was noted. The face was broad and acromegalic with fair, smooth, high-colored skin. The teeth were large and spaced. The fat distribution was of the mons-mammary-girdle type. Some pubic hair was present.

X-Ray Findings.—Skull: negative, no deformities. Sella turcica: normal. Chest: heart and lungs normal. Bone development: All epiphyses are closed; there is an unusual sesamoid bone about the right scaphoid bone; the foot appears rather narrow across the tarsal arch; The wrists are similarly narrow; no skeletal deformities.

Laboratory Data.—Repeated blood counts and urinalyses were all within normal limits. Blood serology was negative. The tuberculin test was negative. The blood

chemistry revealed calcium, 11.2 mg.; and phosphorus, 3.4 mg. The basal metabolic rate was plus 15 per cent, minus 8 per cent, and minus 4 per cent. The glucose tolerance test gave the following values:

	BLOOD SUGAR	URINE	
	(MG.)	SUGAR	ACETONE
Fasting	83	Neg.	++
1 hr.	109	Neg.	Trace
2 hr.	81	Neg.	Neg.
3 hr.	87	Neg.	Neg.

Electroencephalographic Findings.—The examiner reported as follows: "A six-lead monopolar study was done. The record is good technically. There is a persistent ten per second rhythm seen especially in the occipital leads. There is an occasional slower wave, but this is certainly not marked. Hyperventilation slows the record moderately but not unduly. There are no localized abnormalities. This single tracing is within normal limits."

Psychometric Examination.—On the new Stanford-Binet test, Form M, the girl had an I.Q. of 73.

Social Maturity Test.—On the Vineland social maturity scale, the girl had an S.Q. of 80.

Psychiatric Examination.—The girl was pleasant and cooperative to the best of her ability, which however, was definitely limited. Her memory was poor and her judgments were worse. She was very sluggish and phlegmatic and had absolutely no insight into her condition. There were no evidences of visual or auditory hallucinations or paranoid ideas. Her emotional responses were superficial; her entire behavior can best be described as immature.

COMMENT

These cases present a combination of obesity, genital dystrophy, dwarfism, deafness, mental retardation, syndactylism, and familial occurrence. In addition, the patient in Case 2 presents the symptom of tapitoretinal degeneration. These two patients can therefore be considered as cases of "incomplete" Laurence-Moon-Biedl syndrome. The term "incomplete syndrome" is used even though most of the originally required cardinal symptoms are present, the single exception being retinitis pigmentosa. There is, however, an additional symptom present; namely, nerve deafness. The combination of symptoms as reported in these cases has never been described before. Weiss,[4] in 1932, reported one patient with obesity, genital dystrophy, dwarfism, deafness and mental deficiency; however, syndactylism was not present in this patient.

In analyzing more specifically the 102 cases reviewed by Warkany and co-workers,[2] it was seen that the symptoms most frequently present are obesity (seventy-six patients), retinitis pigmentosa (seventy-one patients), and poly- or syndactylism (seventy patients). Next in order are mental retardation (sixty-four patients) and genital dystrophy (fifty-nine patients). Deafness was reported in only four patients. Thus retinitis pigmentosa was absent in thirty per cent of the cases, while in less than 4 per cent of the cases was deafness included as one of the major symptoms. Therefore a symptom complex with deafness appeared to be a rather rare occurrence.

Typical Fröhlich's syndrome (obesity, genital dystrophy, dwarfism), as noted in these patients, was reported in only eleven cases in the literature, whereas the so-called atypical Fröhlich's syndrome (obesity and genital dystrophy) was present in fifty-three patients. The relatively frequent occurrence of obesity in the Laurence-Moon-Biedl syndrome was originally responsible for the assumption that the pathologic changes in this disease occur in the pituitary gland or in the hypothalamus. This theory, however, does not appear valid, since it offered no explanation for the pathology producing the retinitis pigmentosa and the other congenital deformities, such as poly- or syndactylism, etc.

Many other speculative theories have been proposed to explain the pathology of the syndrome, but up to the present time the answer is still unknown. Among the most widely accepted theories is the one of Biedl,[3] who suggested that the syndrome is a familial form of dystrophia adiposogenitalis of cerebral rather than of pituitary origin.

One of the latest theories was put forward by Jenkins and Poncher[5] in 1935. Their explanation was that the syndrome is an interplay of the least three genetic factors: one being responsible for the obesity, genital dystrophy and dwarfism; another for the retinitis pigmentosa; and still another for the congenital deformities, such as poly- or syndactylism. They were uncertain whether the mental deficiency in these cases is due to one of these genes or is dependent on a linked gene.

In general, this theory does not differ grossly from that of Biedl, except that Biedl looked at the retinitis pigmentosa as one of many congenital deformities, and classified this symptom in the same group with poly- or syndactylism, congenital nystagmus or strabismus, atresia ani, deafness, etc. One phase of the pathology, however, seems to be fairly well established; namely, that the Laurence-Moon-Biedl syndrome is clinically not a progressive disorder but instead one large combination of many heredofamilial deviations. This point is immensely important in the diagnosis as well as in the differential diagnosis of this syndrome.

In these patients the typical Fröhlich's syndrome together with the increased sugar tolerance and the delayed bone development seemed to confirm Jenkins and Poncher's[5] assumption that these symptoms are produced by one separate genetic factor, probably pituitary or hypothalamic. However, the results of the electroencephalogram in Case 1 together with the scattered neurologic findings seem to indicate a cerebral factor. The mental retardation and the deafness present in both patients can also be explained on these grounds, while the syndactylism is probably due to another genetic factor.

Although all the symptoms in these cases are self-explanatory and permit the diagnosis of "incomplete" Laurence-Moon-Biedl syndrome, there are several very interesting observations which are worth while discussing.

The electroencephalograms which are reported in this syndrome for the first time show abnormalities in Case 1 which are consistent with a

rather severe cerebral dysrhythmia. However, no definite classification or localization was possible. This fact and the further fact that there are no epileptic waves in the record are of great importance for the differential diagnosis. Convulsive outbreaks or epileptic seizures have never been reported in the Laurence-Moon-Biedl syndrome, and the results of the electroencephalograms are consistent with this statement.

Mental retardation is one of the cardinal symptoms of this syndrome. However, it should be mentioned that the mental retardation is not necessarily of a severe degree; in other words, the child does not have to be feebleminded in order to be considered as fulfilling this major requirement of the syndrome. The degree of the mental retardation seems to be correlated with the severity of the other symptoms present. Thus if a child presents a mild case of this syndrome, the mental retardation need not be so marked. In our cases, the I.Q.'s of 79 and 73, respectively, rank the children as borderline cases of possible mental deficiency.

From the differential-diagnostic point of view it is important to stress the fact, as Ritter[6] has pointed out, that the psychic disorders in the Laurence-Moon-Biedl syndrome are always essentially those of feeblemindedness. Since this syndrome is not a progressive disorder, psychic disorders similar to those of an organic dementia (in form of acute mental disturbances) are not found.

In this connection the discrepancy between the low I.Q. and the normal S.Q. should be commented on. Lurie and co-workers[7] in their study on "Intelligence Quotient and Social Quotient" found that "children with low I.Q.'s tend to compensate for their retardation by the development of a social maturation beyond the level of their intellectual status and that these tendencies on the part of the individual himself are aided by educational practices followed both in the home and in the school. This tendency to compensate was found to be true regardless of the problem the child presented and regardless of the final diagnosis made on the child; the only exception being in the cases of psychotic children." Psychotic children were found to have S.Q.'s lower than their I.Q.'s, which means that they did not compensate socially for their mental retardation. The fact that these patients compensated for their mental retardation by acquiring higher S.Q.'s is also of importance for the differential diagnosis because it seems to confirm the fact that both patients have never been acutely disturbed mentally and at no time could be considered psychotic. It also shows that there was no progression in their mental retardation.

The androgen test also reported for the first time in this syndrome revealed extremely low values; this corresponds with the marked genital dystrophy present in the patient in Case 1. It indicates a gonadal dysfunction which in turn might be linked to a pituitary insufficiency. In Case 2, the estrogen deficiency is indicated by the history of delayed onset of menstruation, its irregularity, and the markedly scanty flow.

Other symptoms of pituitary dysfunction are the obesity, dwarfism, increased sugar tolerance, and retarded bone development.

A careful heart examination and an electrocardiographic tracing revealed normal findings, thus excluding the possibility of congenital heart disease occasionally reported in cases of the Laurence-Moon-Biedl syndrome.[8, 9]

Both the nonprotein nitrogen and the Mosenthal tests were found to be within normal limits and thus failed to demonstrate possible disturbances in the water metabolism or renal damage as reported by several authors.[10, 11]

The roentgenograms showed no skull deformities or skeletal defects. This, in connection with the normal blood chemistry findings (calcium, phosphorus, and cholesterol), demonstrated clearly the absence of bone pathology and of pathologic changes of the lipoid and cholesterol metabolisms.

Differential Diagnosis.—From the differential-diagnostic point of view, the following conditions should be considered:

Juvenile Familial Amaurotic Idiocy (Vogt-Spielmeyer Disease).—As pointed out by one of us in another paper,[12] the early stages of this disease sometimes produce a clinical picture similar to that of the Laurence-Moon-Biedl syndrome, especially when poly-or syndactylism are absent in the latter. However, clinically, the Vogt-Spielmeyer disease is a progressive disorder which is not true of the Laurence-Moon-Biedl syndrome. The average age of patients suffering from the Laurence-Moon-Biedl syndrome is more variable and, in the majority of cases, is higher than that in Vogt-Spielmeyer disease. The obesity and mental retardation (together with poly- or syndactylism or other congenital deformities) in the Laurence-Moon-Biedl syndrome are manifest in early childhood, while on the other hand the patients with Vogt-Spielmeyer disease develop normally in every respect up to the time of the second dentition, and then the characteristic symptoms begin to appear. Hearing was never found to be impaired in patients with Vogt-Spielmeyer Disease. The mental symptoms in the Laurence-Moon-Biedl syndrome are essentially those of feeblemindedness, whereas the mental symptoms in Vogt-Spielmeyer disease are similar to those of an organic dementia. Furthermore, there is a gradual but continuous deterioration of the intellect in children suffering from Vogt-Spielmeyer disease, while in the Laurence-Moon-Biedl syndrome the intellectual level, though low, always remains at approximately the same level without showing any regression. Furthermore, the repeated convulsive outbreaks which occur in more than 80 per cent of all patients with Vogt-Spielmeyer disease and which can be demonstrated on electroencephalographic tracings, have never been reported in cases of the Laurence-Moon-Biedl syndrome. Finally, the clinical picture of the Vogt-Spiel-

meyer disease is very uniform (one author speaks of the "photographic similarity"[13] of all the cases) and very seldom show combinations of different clinical symptoms.

Schüller-Christian Disease or Xanthomatosis[14] may in some respects appear similar to the Laurence-Moon-Biedl syndrome. Typical Fröhlich's syndrome, mental retardation, and deformities of the skull may be present in both disorders. However, in addition to these symptoms, the Schüller-Christian disease usually shows various other symptoms such as exophthalmus, diabetes insipidus, generalized xanthomatosis, and numerous skeletal defects which have never been reported in the Laurence-Moon-Biedl syndrome. Furthermore, in the Schüller-Christian disease there is an alteration of the lipoid and cholesterol metabolisms, evidenced by an increase of the blood lipoids, especially the blood cholesterol.

Juvenile Dementia Paralytica[15] can be definitely differentiated by means of serologic tests, the presence of syphilitic stigmata (Hutchinson's teeth, osteitis or periosteitis, saddle nose, interstitial keratitis, etc.) and the neurologic findings which are typically pyramidal.

Cerebral Sclerosis of Scholz[16] is characterized by a very rapid course and absence of degenerative retinal changes and deafness.

SUMMARY

Two cases of "incomplete" Laurence-Moon-Biedl syndrome, showing an unusual combination of heredofamilial deviations, are reported, and the diagnosis, pathology, and differential diagnosis of this disorder are discussed.

The electroencephalographic findings as well as the results of the androgen, audiometric, and social maturity tests are reported for the first time in this condition.

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American Academy of Pediatrics

Proceedings

ELEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOSTON, MASS., OCT. 9-11, 1941

Round Table Discussion on Chemotherapy

Chairman: John A. Toomey, M.D.

Associates: Maxwell Finland, M.D., Assistant Professor of Medicine, Harvard Medical School, Boston, Mass.
Harrison F. Flippin, M.D., Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
George M. Lyon, M.D.
Conrad Wesselhoeft, M.D., Clinical Professor of Communicable Diseases, Harvard School of Public Health, Boston, Mass.

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Sulfanilamide in Scarlet Fever

Conrad Wesselhoeft, Boston

The tremendous advances made in chemotherapy have been accompanied by equally extravagant claims. The literature from the start has been filled with bald and sweeping assertions.

Much attention has been devoted to the manner of administration, but less attention has been paid to the pitfalls in the interpretation of results. Gradually we are beginning to acquire a more detailed evaluation of these drugs. Because beta hemolytic streptococci were among the organisms most susceptible to the sulfonamides, it was assumed that all diseases caused by these organisms would respond equally. Thus it is that scarlet fever is coupled with erysipelas as diseases in which sulfanilamide is useful. This is very misleading. The rash and the initial pyrexia of scarlet fever are in no way influenced by these drugs, while in erysipelas the lesion and the fever respond promptly. The reason given for this is that the infection in the fauces in scarlet fever is superficial; the toxin absorbed from this area has a remote effect on the superficial capillaries of the skin as manifested by the characteristic rash. In erysipelas, on the other hand, the streptococci are

deep in the layers of the skin. Consequently sulfanilamide has a much more difficult time reaching the streptococci in the eruptive phase of scarlet fever than it does in erysipelas. Therefore the response is not equal.

The deeper the streptococci penetrate into the tissues in scarlet fever, the more pronounced is the beneficial action of chemotherapy. Today, patients rarely die of the eruptive stage of scarlet fever. They die of the complications resulting from the deep invasion of the streptococci. The mortality of meningitis and bacteremia in scarlet fever has been tremendously reduced, with the result of a general lowering of the mortality of scarlet fever. Thus, the general mortality of scarlet fever, which has been between 2 and 3 per cent before the introduction of chemotherapy, is now a fraction of 1 per cent.

It is important to take up the detals of the results of chemotherapy not only in each disease, but also in the various manifestations of each disease. When we do this in a disease like scarlet fever, we find that many sweeping assertions are misleading. It is quite impossible to evaluate the action of a drug in a given condition without taking into consideration the factors involved in bringing about the condition. We must differentiate between toxic scarlet fever and septic scarlet fever, the former being the result of the toxin and the latter being the result of the pyogenic properties of the streptococci. If the eruptive phase is accompanied by sepsis, chemotherapy is likely to be effective. Otherwise it is not.

If the drug has no effect on the eruptive phase, what is the advantage of giving it in this disease? The answer to this is that if it is given during the pyrexia or only for the first week of the disease, it accomplishes little or nothing except in the presence of septic invasion. On the other hand, if it is continued through convalescence, it will reduce the incidence of complications. Nor will all of these complications be of purely pyogenic origin. The most marked reduction will be in the incidence of adenitis; secondly, in the incidence of otitis media and the resulting mastoid. But let it be distinctly understood that in order to bring about the lowered incidence, the drug has to be used in proper dosage and throughout the disease. Such usage will bring rashes, fever, vomiting, and psychoses; but all of these are worth accepting if we can cut down mastoiditis, meningitis, and bacteremia. Acute glomerulonephritis occurs only in 1 or 2 per cent of the cases anyway, and so far chemotherapy has shown no evidence of reducing or increasing this complication. The use of sulfanilamide throughout the course of scarlet fever entails close observation, preferably in a hospital.

The next thing to consider is the effect of sulfanilamide on the complications. It appears to be beneficial in some cases of simple cervical adenitis, but in other cases it is not. It has no effect whatever on suppurative cervical adenitis. I am at present engaged in the study of the effect of sulfanilamide on the course of otitis media, and while the impression was gained at the bedside that chemotherapy is effective in shortening the duration of the discharge from the ear, a further study of these cases shows how easily one can be deceived. In the first place, one must compare results with chemotherapy with results before chemotherapy. If we are not giving chemotherapy and the discharge stops is two or three days, it makes less impression on our minds than if we have given a new preparation and are watching intently for the result.

The incidence of otitis media in scarlet fever in 500,000 cases was 12 per cent. More recently the incidence is nearer 8 per cent with the reduction in the severity of the disease. This incidence is dependent on many factors. First of all, the age of the patient, because a child of 2 years will be apt to have otitis media in almost 50 per cent of the cases, whereas in adults the incidence is from 5 to 7 per cent. Thus there will be a wide discrepancy in the incidence of otitis media reports from an infants' hospital and a military hospital. The season of the year and mixed infections also play an important part.

If we say roughly that we can expect otitis media in about 10 per cent of the patients, we can also say roughly that mastoiditis will occur in 10 per cent of the patients with otitis media. Have we been able to cut this down with the use of sulfanilamide? From my figures, where sulfanilamide has been given, even within twenty-four hours and continued uninterruptedly for the duration of the discharge, it has not reduced the incidence of mastoid below this decimal figure, but it was lower than the concurrent controls who were above average during the period covered. Furthermore, we have seen a number of patients who have gone home with a dry ear following sulfanilamide administration and have returned to the hospital with recurrent suppuration, and some of these have gone on to mastoids. In these suppurative ears under chemotherapy we are impressed by the fact that many of these cases were delayed in coming to a mastoidectomy as a result of prolonged chemotherapy during which the white count and the x-ray evidence of mastoid involvement was concealed. Certainly, in the field of scarlet fever we have much to learn regarding the use of sulfanilamide.

Sulfadiazine

Harrison F. Flippin, Philadelphia

Animal studies[1, 2, 3] have indicated that sulfadiazine[4] may be a chemotherapeutic agent with wide clinical usefulness and probably is less toxic than any of the other sulfonamides now in common use. Observations in man dealing with the absorption, excretion, and distribution of sulfadiazine[5, 6, 7, 8] show that the drug is somewhat less rapidly absorbed from the gastrointestinal tract than is sulfanilamide, sulfapyridine, or sulfathiazole, although higher blood levels are attained and are more sustained than with the other compounds. Approximately 15 per cent of the drug appears in the blood in the conjugated form. In this respect it resembles sulfanilamide, in contrast to higher concentrations of acetylsulfapyridine and acetylsulfathiazole usually found in the blood. Sulfadiazine is excreted almost entirely in the urine, although the rate of excretion is somewhat slower than that of the other compounds. The acetyl derivative of sulfadiazine is quite easily excreted by the kidneys and approximately one-third of the total drug found in the urine represents acetylsulfadiazine. In urine the solubility of acetylsulfadiazine is much higher than that of acetylsulfapyridine or acetylsulfathiazole. Sulfadiazine diffuses readily into the various body tissues and fluids, reaching a concentration in exudates and transudates approximating that obtained in the blood. In contrast to sulfathiazole, about 60 per cent of sulfadiazine passes into the cerebrospinal fluid.

Insufficient clinical data do not permit at this time a comparison of the therapeutic effectiveness of sulfadiazine with the other sulfonamides now in general use. However, personal clinical experience[9, 10] with sulfadiazine combined with the reports of others[2, 11, 12, 13, 14] suggests that this drug is an effective chemotherapeutic agent for the control of certain bacterial diseases. It appears that sulfadiazine is equally effective as any of the other compounds in the treatment of infections due to the pneumococcus, meningococcus, gonococcus, *Streptococcus viridans*, and possibly the *staphylococcus*. Limited experience with its use in severe hemolytic streptococcic infections suggests that sulfadiazine is effective, but until more data are collected, sulfanilamide remains the drug of choice in this type of infection. In view of experimental studies plus several comments in the literature, it appears that sulfadiazine is the superior drug in combating infections due to Friedländer's bacillus, Type B. Preliminary observations also indicate the effectiveness of sulfadiazine in the control of the more common types of urinary tract infections.

Thus far it appears that sulfadiazine is less toxic than sulfanilamide, sulfapyridine, or sulfathiazole. Nausea and vomiting occur in about 4 per cent of the patients and rarely does it become so severe as to necessitate stopping drug therapy. Fever and skin rashes due to the drug have been rare. Renal irritation

with the use of sulfadiazine has been negligible in our experience, although other observers[11, 12] have reported instances of loin pain accompanied with hematuria and patients with blood urea nitrogen retention which may have been due to the drug.[11, 14] In view of the behavior of sulfadiazine in man, plus the higher degree of solubility of acetylsulfadiazine in urine, we should expect less renal irritation with this drug than with sulfapyridine or sulfathiazole. Studies on crystalluria[15] indicate that sulfadiazine-treated patients have fewer crystals in the urine than those receiving sulfapyridine or sulfathiazole. Depression of the white blood cells has been observed in a few instances, but as yet no cases of agranulocytosis have been noted. Acute hemolytic anemia has been reported,[14] and in view of the drug's ability to penetrate readily the red blood cells, this toxic effect should be anticipated. Patients with mental confusion have also been observed, although this toxic effect is difficult to evaluate in seriously ill patients. No doubt other toxic effects will manifest themselves as the drug receives more widespread use.

Sulfadiazine is poorly soluble and hence must be given by the oral route. In general, the dosage is similar to that employed with sulfathiazole except that it is possible to maintain effective blood concentration by administering the drug every sixth hour instead of repeating the dose at four-hour intervals. In certain conditions, such as meningeal infections, where high concentrations of the drug in the cerebrospinal fluid are indicated, it is usually advisable to adhere to the four-hour dose schedule. Because of the slow excretion of sulfadiazine and its low degree of toxicity, a relatively high concentration of the drug in the blood may be attained and maintained without ill effects to the host.

In certain instances where oral therapy is impossible or impracticable, or when a prompt rise in drug concentration in the blood is desirable, the sodium salt of sulfadiazine as a 5 per cent solution in sterile distilled water is employed by the intravenous route. Observations[16] on the use of sodium sulfadiazine intravenously indicate that effective blood levels of the drug are sustained by administering the total twenty-four-hour dosage in divided doses at twelve-hour intervals. Thus the handling of postoperative patients and patients who are unable to take the drug by mouth has been simplified with the advent of this compound.

In conclusion, it may be said that sulfadiazine is apparently an effective chemotherapeutic agent, having a wide range of usefulness, possessing a relatively low degree of toxicity, and, because of its behavior in man, it offers definite advantages over the other sulfonamides now in common use. Thus sulfadiazine may replace sulfanilamide, sulfapyridine, and sulfathiazole as our chief therapeutic reliance in many types of bacterial infections.

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Sulfaguanidine in the Treatment of Acute Bacillary Dysentery

George M. Lyon, Boston

The guanidine analogue of sulfapyradine is known as sulfaguanidine, or sulfanilylguanidine. Marshall, Bratton, White, and Litchfield[1] first directed attention to its possible value as a chemotherapeutic agent in intestinal infections in a paper published in September, 1940.

At the Harriet Lane Home in Baltimore during the summer of 1940, seventeen children with acute bacillary dysentery were treated with sulfaguanidine. The results were described in a paper published in January, 1941, by Marshall, Bratton, Edwards, and Walker.[2] Because of a lack of suitable clinical material, these workers were unable to carry on a controlled study at that time.

During the past year, a group of us living in the "dysentery country" have interested ourselves in an attempt to appraise the value of sulfaguanidine in the treatment of acute bacillary dysentery.

At first the chemical was studied in a small well-controlled series of carefully selected patients having the disease in a severe or moderately severe form. In all of these, treatment was instituted during the first week of fever or diarrhea. The observations and the conservative conclusions drawn therefrom have been reported.[3]

I have prepared for your convenience today a summary of that study.

Next we subjected sulfaguanidine to the practical test of wide-scale use in the treatment of all forms and stages of acute bacillary dysentery as they were encountered in actual clinical practice in the office, home, and hospital of our part of the country.

In excess of 300 patients with acute bacillary dysentery, with fever and with blood, pus, and mucus in the stools, have been treated with sulfaguanidine within the last thirteen months. The patients included in this series were those typical of the character and incidence of "bloody flux" as observed in our mining and rural mountainous sections in which acute bacillary dysentery continues to be an important endemic disease, affecting particularly, but not by any means exclusively, infants and young children. Most of the positive stool cultures revealed the Flexner bacillus. Dr. Lon C. Hall, of Paintsville, Ky., observed the successful use of sulfaguanidine in a series of Hiss Y infections, while Dr. E. C. Richards, of Gallipolis, Ohio, besides observing its efficacy in the treatment of Flexner infection, also successfully treated one patient with Shiga infection. These patients have been included among the 300 already referred to as having been treated with sulfaguanidine.

Our experience indicates that in this form of acute bacillary dysentery, sulfaguanidine, when given early in the disease, is a safe, rapidly effective, if indeed not actually a genuinely specific, chemotherapeutic agent.

When treatment with sulfaguanidine was begun within five days of the onset of fever or of diarrhea, an early termination of the clinical course of the disease resulted with almost uniform regularity. The diarrhea was controlled, the infection was overcome, and the patient was clinically almost entirely well within forty-eight to seventy-two hours after the institution of chemotherapy. Only occasionally did it require as long as four to five days. Remarkable recoveries within twenty-four to thirty-six hours were indeed not unusual.

No deaths have occurred in patients in whom there was no concomitant infection or disease and in whom chemotherapy was started within five days of onset of fever or diarrhea. A possible exception to this may have been a patient of Dr. L. C. Hall's. This patient had barely recovered from a nearly fatal diarrheal disease of unknown etiology just shortly before the onset of the final illness of dysentery.

A state of "postdysentery" intestinal indigestion frequently develops in patients who have had acute bacillary dysentery. This is known to be particularly liable to happen in infants and young children. Indeed it may be so severe or so stubborn as to be fatal. We have not seen this develop in a single instance in patients in whom treatment with sulfaguanidine was started within five days of the onset of fever or diarrhea, unless perhaps there may be some exceptions in those incurring the disease during the neonatal period. When employed in the dosages used by us, that is, 0.05 Gm. per kilogram of body weight every four to six hours, and when used in the manner described, toxic effects were so rare as to be truly negligible.

Where treatment with sulfaguanidine was instituted somewhat later (six to ten days), the results were not, in general, quite as striking as when chemotherapy was begun earlier. One must be cautious, however, in attempting to evaluate the effectiveness of the drug in patients who have been ill for more than five days, because in a certain percentage of the milder cases, recovery does take place spontaneously between the fifth and tenth days. The more usual case, however, is the one in which the disease is quite as active during the second five-day period as during the first five-day period. To one familiar with acute bacillary dysentery in infants and young children, it is readily understandable that certain of the patients might not respond well to chemotherapy because of the extensive chemical pathology which may have been established by the primary bacterial infection. In the smaller infants in whom an advanced state of fluid imbalance, intoxication, or other complication of bacillary dysentery had already intervened before the institution of treatment, it was generally possible to clear up the diarrhea in short order and to improve the clinical picture, but measures other than the administration of sulfaguanidine were required for the correction of such complicating conditions. Even in these patients, however, the death rate was remarkedly reduced and, in general, the clinical course greatly shortened. Deaths in this group occurred almost exclusively in patients who were moribund on admission, such taking place usually within twenty-four hours and rarely more than forty-eight hours after admission. In these patients severe dehydration, intoxication, and/or acidosis were invariably present to an extreme degree. As a rule, if there were still blood and pus in the stools and if extreme states of fluid imbalance or acidosis had not already developed, the results were almost as satisfactory in the patients in whom treatment was first instituted during the six- to ten-day period as it was in those in whom chemotherapy had been begun at an earlier date. Indeed, at times the management of the diet, of the fluid intake, and of other properly indicated therapeutic measures appears to be much more important in the patients not treated until the sixth day than it does in those treated earlier. Such measures must accompany the chemotherapy if the best results are to be obtained.

Where chemotherapy was not instituted until after the tenth day, the response was, in general, quite similar to that in the patients of the group just described. If an advanced state of abnormal physiologic function or chemical pathology had already developed, results were in large measure in direct proportion to our ability to correct these altered states. In these patients, as in the former group, when a death occurred it usually took place shortly after admission to the hospital. If blood or pus were present in the stools, it was generally possible to clear up this condition and the diarrhea within seventy-two hours. If we could correct the dehydration, fluid imbalance, and general intoxication, we obtained a good end

result. In this group of patients, without chemotherapy one would have expected the disease to be attended regularly by a long period of illness, often of many weeks' duration and there would have been a relatively high death rate. In such patients, however, when sulfaguanidine was employed, we very frequently observed a significant reduction in the duration of the illness. Chemotherapy was effective in controlling the activity of the infection, although it alone did not correct damages already brought about, or set in motion, by the infective process. By this I mean such things as severe intestinal indigestion, advanced states of chemical pathology, fluid imbalance, acidosis, etc. These all require special therapeutic management just as in the days before the introduction of sulfaguanidine. The prevention of these states is possible by the administration of the drug during the first five days of illness in almost every instance.

I explain the above in such detail because many may fail to realize that in bacillary dysentery, particularly in infants and young children, there is the acute stage of active bacterial infection characterized by fever, diarrhea with blood and pus, and varying degrees of disturbance of digestion and that this stage is frequently, but not invariably, followed in varying degrees of time by such altered physiologic states as severe intestinal indigestion, fluid imbalances, acidosis, and other chemicopathologic states which result from the damage by the infection or the intoxication resulting therefrom. Sulfaguanidine without question effectively controlled the infection and arrested its further damage. It quite as definitely did not by itself undo the harm already brought about by the activity of the bacilli or their toxins, once such damage had occurred.

Death may occur early, before the advent of fluid imbalance and acidosis. In such instances it is due to the toxemia resulting from the invasion of the body by the dysentery bacilli. A more common cause of death, however, is the complicating intoxication, fluid imbalance, and acidosis which may accompany, or follow, the damages produced by the bacilli or the toxemia resulting therefrom within the body. Sulfaguanidine, if given early enough, was effective in preventing death from toxemia in the malignant, rapidly fatal form, and by arresting the infection, it was effective in preventing fluid imbalance and acidosis from developing in the less malignant forms. In some few instances when fluid imbalance and acidosis had occurred, sulfaguanidine, by arresting the activity of the infection, enabled the natural physiologic powers of the body to work to the best of their ability in correcting the abnormal physiologic states which had arisen. Sulfaguanidine does provide much better opportunities for the physician to overcome these unfavorable physiologic states through the use of such measures as the provision of proper fluid intake, glucose, saline, calcium gluconate, blood serum, or whole blood transfusion. Sulfaguanidine by itself will not take the place of these measures.

In those instances where there is a persistent inability to digest and to assimilate food, the condition presented must be considered to be an expression, directly or indirectly, of the damage already produced within the body by the invasion of the dysentery bacilli. If the infection has already subsided and those conditions so characteristic of a postdysentery infection state are present, sulfaguanidine alone is not effective, nor should one expect it to be so. If given early, sulfaguanidine will almost invariably prevent the development of advanced chemical pathology. On the other hand, if infection is still present and these states occur, sulfaguanidine, by arresting the infection, provides opportunity for nature, or the physician, to correct more effectively chemical pathologic states which have arisen. Because this is true and because it is frequently so difficult to know whether the infection is still active or not, and as sulfaguanidine is so free from toxic effects when it is used as we have used it, it would seem logically indicated that sulfaguanidine be given for from three to five days to those patients who have the complications which so frequently are

seen to accompany or follow acute bacillary dysentery, even though one feels that the active infection has subsided. We have repeatedly seen a beneficial result follow the use of sulfaguanidine in such instances. We have also had ample opportunity to observe its freedom from toxic or harmful effects on these already greatly damaged infants who are probably quite susceptible to further injury, be it chemical or otherwise.

Sulfanguanidine rarely needs to be given for more than five days. Not infrequently its administration for only three days is sufficient. As we have had more and more experience with the drug, we have become convinced of the fact that a shorter period of treatment almost invariably suffices the need, rarely exceeding five days. If a satisfactory result is not obtained in from five to seven days, one may employ sulfathiazole instead for a like period. This has been recommended[4] but in my own personal experience has rarely been necessary. When so employed, sulfathiazole yielded no strikingly better results. Such may, however, not be the case in chronic bacillary dysentery.

Toxic effects as a result of the chemotherapeutic agent were so rarely observed as to be truly negligible. They were much less frequent than would have occurred with the use of either sulfathiazole or sulfanilamide.

Enough older children and adults have been treated with sulfaguanidine to enable us to say that it is entirely as effective in the treatment of acute bacillary dysentery in them as in the treatment of infants and young children.

While it may not be absolutely necessary to change the diet radically when administering sulfaguanidine to patients with acute bacillary dysentery, there are some reasonably acceptable observations which seem to indicate that a soft, bland diet somewhat restricted in amount probably does aid materially in the effectiveness and the promptness of the chemotherapy in bacillary dysentery. I have a distinct impression that the cultured lactic acid milk and a diet relatively high in protein combined with a moderate restriction in amount offer the best results, particularly in the smaller children and infants. The importance of ample fluids by mouth or otherwise is obvious. Glucose solution may be given orally to advantage. Very rarely has it been observed to aggravate the diarrhea. At times physiologic solution of sodium chloride and even some calcium gluconate may be given to advantage orally or otherwise. In general, the short course of the illness under the influence of early chemotherapy renders the matter of nutrition of less importance than it would be in the longer, more protracted courses of the disease so frequently encountered when the patient has not had the benefit of chemotherapy.

Since we have made the above observations to the probability of a better and more prompt therapeutic effect in those patients who were receiving a moderately limited diet and a diet which was likewise high in protein (mainly casein), Rosenthal[5] has reported during the last month some laboratory findings which clearly suggests the possible relationship of both quality and quantity of the food in the diet to the toxic or therapeutic effects of the chemotherapeutic agent employed. When sulfanilamide is given to rats, a low food intake enhances the toxicity effect. Likewise in animal experiments, protein inhibits the toxic and the therapeutic effects of sulfanilamide, even when the drug is given subcutaneously instead of orally. There may be good reason to pay more attention to diet when the sulfonamides are used than perhaps we recognize at the moment.

We have not had a sufficient experience with the chronic forms of bacillary dysentery to make a statement. On the other hand, what experience we have had has tended to be favorable, although less striking in nature.

Acute bacillary dysentery is now a disease which can be successfully treated chemotherapeutically. While we have had very favorable results with sulfathiazole, we have had even better results with sulfaguanidine. In our experience it has been possible to clear up the infection and the activity of the disease in from one

to two days earlier with sulfaguanidine than with sulfathiazole. Although sulfathiazole is not very frequently accompanied by vomiting or other toxic effects, these and other toxic manifestations are almost never encountered with sulfaguanidine when given in the manner previously described.

Chemotherapy has completely revolutionized the treatment of acute bacillary dysentery. "Bloody flux" will not be the killer of infants and young children in the future that it has been in the past, nor need our armed forces ever again be seriously handicapped by the ravages of "bloody flux."

The increased use of sulfaguanidine by the physician and his realization of the effectiveness of early chemotherapeutic treatment of "bloody flux" will result in an increasingly larger and larger reduction in the mortality from the disease at all age limits. A public health education program which will teach parents the value of early treatment may be employed to advantage in getting the patients to the physicians early so treatment can be started early.

In regard to the simple diarrheas of apparently unknown etiology and to the so-called "parenteral diarrheas," it is quite difficult to make an honest appraisal of the effectiveness of sulfaguanidine or any other therapeutic agent. There are many important limitations associated with a careful appraisal of the treatment of diarrheas of this type, particularly those relating to etiologic cause and to proper classification by different workers. It is, however, fair to say that we have been making some reasonably careful observations and have arrived at some fairly good "clinical impressions." We feel that even in the treatment of the so-called simple diarrheas, generally considered not to be infectious in nature, that sulfaguanidine may have a place. In such instances our experience with sulfaguanidine has been similar to that of Davison and his co-workers at Duke University in the use of sulfathiazole. Sulfaguanidine appears to be effective in many, but by no means all of the simple or parenteral diarrheas. Many of these so-called simple diarrheas are, of course, instances of bacillary or other bacterial or infectious diarrheas, even though they have no blood or pus in the stools. Certainly in most apparently simple diarrheas that persist for more than forty-eight hours, it appeared not at all illogical to use either sulfaguanidine or sulfathiazole. At such times a treatment period of three days has usually sufficed. The dosages employed were the same as those employed in treatment of acute bacillary dysentery. I am not prepared to say whether sulfaguanidine or sulfathiazole would be the more effective in the majority of simple diarrheas. If known to be associated with infections located outside the intestinal tract, sulfathiazole would appear to be the one of choice. It is fortunate for us that we have two agents which are effective not only in treating acute bacillary dysentery, but also indeed in treating many of the apparently simple diarrheas.

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Comparison of the Common Sulfonamides*

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For purposes of orientation in the discussions and in the answers to questions which are to follow, I have tried to summarize the present views on the effectiveness

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TABLE I

RELATIVE EFFECTIVENESS OF FOUR COMMON SULFONAMIDES AGAINST CLINICAL INFECTIONS WITH THE MOST COMMON BACTERIA

ORGANISM	SULFANILAMIDE	SULFAPYRIDINE	SULFATHIAZOLE	SULFADIAZINE
Hemolytic streptococcus	+++	+++	++	++++
Pneumococcus	+	+++	++++	++++
Meningococcus	++++	++++	++++?	++++?
Gonococcus	+++	+++	++++	+++?
Staphylococcus	+	+	+++	+++
Colon bacillus	+	+	+++	+++
Friedländer's bacillus	0	+	+	++

TABLE II

RELATIVE TOXICITY OF FOUR COMMON SULFONAMIDES

TOXIC EFFECT	SULFANILAMIDE	SULFAPYRIDINE	SULFATHIAZOLE	SULFADIAZINE
Nausea and vomiting	+	++++	+++	+
Cyanosis	++++	+	0	0
Anemia	++++	++	0	0
Leukopenia	+++	++++	+	+
Dermatitis	+++	++	++++	++
Fever	++++	++	+++	+
Urinary tract	0?	++++	++++	+
Hepatitis	++	+	0?	0
Nervous	++	+	+	0?
Mental	+++	++	+?	+?

(Table I) and relative toxicity (Table II) of the four common sulfonamides that have received wide use. I am including sulfadiazine because, although it has not yet been used as widely as the other three drugs, it gives promise, as Dr. Flippin has pointed out, of replacing all of the others for most purposes. It should be borne in mind that the number of plus signs in these tables is only relative, and they represent only a rough evaluation, which in each instance is subject to change as further information becomes available. This evaluation is based largely upon our own experience, coupled with our interpretation of the reports as they appear in the literature.

Sulfaguanidine is omitted from the tables because we have not had enough experience to permit us to express opinions. It is my understanding from a few observations that some of my colleagues have made, as well as from some of Dr. Marshall's recent statements, that sulfaguanidine may, especially when the dosage is not adjusted properly, give all of the toxic manifestations that are commonly seen with other sulfonamides. This is particularly true when doses are spaced at short intervals. There is also some reason to believe that nervous and muscular reactions may be more common, although mention of this has not yet been made in the literature.

Dr. O. L. Peterson and I have recently reviewed the available data concerning the urinary tract in relation to sulfonamide therapy.* It would appear that sulfanilamide, because of its greater solubility and lesser tendency to produce crystalline concretions, hematuria, etc., would be the drug of choice in all patients in whom impairment of renal function is known or suspected. This is particularly true of cases of acute nephritis. Most clinicians with wide experience, however, have had occasion to use each of the other drugs in such cases under very close supervision and have had favorable results with a minimum of difficulty. Of

*Am. J. M. Sc. 202: 757, 1941.

course it is important, when using sulfanilamide, to be sure that it is being used for an organism against which it is effective. It would be particularly useful for hemolytic streptococcal infections which are most commonly associated with acute hemorrhagic nephritis. With other organisms, such as the staphylococcus or the pneumococcus, it may be necessary to resort to the other drugs which are efficacious against that organism. Under these conditions, provided the renal damage is not too great, improvement of renal function most often occurs coincident with improvement in the bacterial infection. Sulfadiazine would appear at present to be the drug of choice because of the low percentage of acetylation in the urine and the higher solubility of the acetylated form of the drug in the urine as compared with sulfapyridine and sulfathiazole. Its wide range of effectiveness, which includes hemolytic streptococcus, makes this drug desirable under these conditions.

In the treatment of meningitis since the introduction of sulfathiazole, the comparative levels in blood and spinal fluid have been emphasized, because with this drug the concentrations in the spinal fluid are usually only about one-third of those found in the blood. All other drugs are found in the cerebrospinal fluid in concentrations two-thirds or more of those in the blood. It is not known, however, whether this difference is significant, since sulfathiazole has been used with good results by a number of physicians for the treatment of meningococcal and other meningitides.

DISCUSSION

DR. JACK CHESNEY, KNOXVILLE, TENN.—What is the effectiveness of the sulfonamides in gonoccus vaginitis and ophthalmia?

DR. FLIPPIN.—Sulfathiazole is effective in vaginitis combined with the use of hormone therapy; also in occlusion blennorrhea. Dosage is ½ gr. four times a day for one week. Rest, 7 to 10 days. If necessary, repeat this course.

DR. J. E. BROWN, JR., COLUMBUS, OHIO.—What about the use of alkalies? Is the incidence of renal complications less?

DR. FLIPPIN.—Usually there are fewer crystals in the urine when alkalies are given. This is less true with sulfadiazene on account of its greater solubility.

CHAIRMAN TOOMEY.—In experimental works in monkeys fewer crystals are found when alkalies are not given than when they are. The giving of plenty of water is the important factor.

DR. FLIPPIN.—The administration of fluids is of extreme importance. Diuresis decreases the concentration of the drug in the blood very little. Forced fluids are important in giving all the sulfonamides except sulfanilamide which does not crystallize in the renal tubules.

DR. M. A. PERLSTEIN, CHICAGO.—What is the drug of choice in treating influenzal meningitis?

DR. FINLAND.—There are some reported cures from drugs alone. The most effective one is as yet questionable. The combined use of specific Type B rabbit serum is most effective.

CHAIRMAN TOOMEY.—Massive doses must be used to be effective.

DR. H. T. VOGEL, JACKSON HEIGHTS, N. Y.—What is the effect of these drugs in virus diseases?

CHAIRMAN TOOMEY.—Ineffective so far. Experimental animals die quicker. May be effective in trachoma.

DR. TRASK, NEW HAVEN.—What is the prophylactic value in scarlet fever contacts?

DR. WESSELHOEFT.—According to Hoyne, they are ineffective. Their effect in "return cases" is inconclusive.

DR. CHESNEY.—What is the most effective form of treatment of meningococcus meningitis, with serum alone, drugs alone, or both?

DR. FINLAND.—According to Banks, mortality with drugs alone is 10 per cent, with serum alone, 30 per cent. Probably the safest method at present is to give serum, if improvement is not marked after twenty-four hours of drug therapy. Serum given intrathecally is very irritating.

CHAIRMAN TOOMEY.—Our last thirty-five patients all recovered without complications with the use of 100,000 units of serum with massive doses of drugs. Two of these were septic cases.

DR. FINLAND.—It is worth while to give serum even if only 1 out of 10 is saved who would not be otherwise.

DR. FLIPPIN.—The routine treatment at the Philadelphia General is: (1) All patients are given S-diazene. (2) All patients with positive blood cultures are given serum. (3) All patients who do not respond favorably to drugs in thirty-six hours are given serum. Sixteen cases in pregnant women recovered with drug therapy alone.

CHAIRMAN TOOMEY.—What have been the results of chemotherapy of this type in measles and pertussis?

DR. WESSELHOEFT.—(1) In measles, ineffective in the eruptive stage; (2) Lowers incidence of broncho-pneumonia; (3) In pertussis, incidence of pneumonia reduced.

DR. S. S. CHIPMAN, NORWALK, CONN.—What about the use of sulfathiazole topically?

DR. FINLAND.—It has been used effectively as a prophylactic in wounds and cavities and by irrigation. Sulfanilamide is the drug of choice because of its greater solubility; 1 per cent in body fluids. Sulfathiazole, which is relatively insoluble, may act as a foreign body when used as a powder. In topical use, effect is only on the surface in addition to that absorbed. In the nasal cavities a 5 per cent solution of sodium sulfathiazole has been used but may be irritating. A ½ per cent solution in salt is just as effective.

DR. G. C. MALLEY, ZANESVILLE, OHIO.—What about its use in furunculosis?

CHAIRMAN TOOMEY.—There is very little effect. The pyogenic membrane acts as a barrier to diffusion of the drug.

DR. FINLAND.—In furunculosis and empyema an inhibiting substance is present in the pus. Huge doses of drugs are necessary to be at all effective. Packing an opened furuncle may be effective.

DR. J. P. SCOTT, PHILADELPHIA.—A 5 per cent emulsion of sulfathiazole in vanishing cream is effective in impetigo. Dr. Donald Pillsbury, a dermatologist in Philadelphia, used this in a large series of cases with unusual success. His patients showed no detectable level in their blood. His cases are not published at this date, but the paper is in press. The composition of this vanishing cream is not known to me. I doubt if the manufacturer will divulge it. I do know that

most vanishing creams consist of about 25 per cent stearic acid in water, with a small amount of some alkali such as potassium hydroxide. Since June 1, I have personally used it on about fifteen to twenty patients with impetigo and have felt that it was better than other applications I had used prior to this time.

DR. PERLSTEIN.—A 5 per cent emulsion in K-Y jelly is also effective in impetigo.

DR. TRASK.—What of drug effectiveness (sulfaguanidine) in typhoid and paratyphoid?

DR. LYON.—There is no striking effect on the course of typhoid except that the sensorium is clearer and the appetite better. In paratyphoid, one-third of the patients are benefited as in dysentery.

DR. TRASK.—What about diphtheria?

DR. WESSELHOEFT.—There is no effect either in vivo or in vitro.

DR. WESSELHOEFT.—When should drug therapy be discontinued in meningitis?

CHAIRMAN TOOMEY.—First give 100,000 to 150,000 units of serum intravenously. Then drug doses large enough to obtain a concentration of 10 to 15 mg. per cent in the blood for four days. If clinically better, gradually reduce the dose but continue treatment over a period of fourteen days.

DR. FINLAND.—In staphylococcus meningitis continue treatment for three or four weeks and obtain a normal spinal fluid for one week.

DR. F. H. MATTHEWS, MONTCLAIR, N. J.—What of the use of sulfaguanidine in undulant fever?

DR. LYON.—We have had no experience with its use.

DR. M. B. LOW, GREENFIELD, MASS.—(1) In scarlet fever does the full dose have to be given for seventeen days? (2) If a child in a family gets scarlet fever or meningitis, would sulfanilamide help other members of the family in prophylaxis?

DR. FLIPPIN.—(1) Yes. (2) Sulfanilamide is not of use prophylactically.

DR. P. M. STIMSON, NEW YORK CITY.—What is your dosage of sulfanilamide in scarlet fever? How do you cut down the incidence? How do you differentiate between the toxic cases in the beginning and the septic cases?

DR. WESSELHOEFT.—Normal adult dose, total of 120 gr. in twenty-four hours. Child, 40 to 60 gr.

DR. HARRY LOWENBERG, JR., PHILADELPHIA.—Can exfoliative dermatitis or generalized lymphadenopathy and hepatosplenomegaly appearing one week after sulfathiazole therapy has been stopped be considered a toxic effect of the drug?

DR. FLIPPIN.—This case is due to sulfonamide toxicity.

CHAIRMAN TOOMEY.—What has been your experience, Dr. Kramer, with chemotherapeutic agents in the treatment of virus diseases?

DR. SIDNEY KRAMER, BOSTON.—They are of no proved value. My work has been with the virus of poliomyelitis.

CHAIRMAN TOOMEY.—I agree too that the sulfonamides have no effect on the virus of poliomyelitis.

DR. CAREY.—Will you briefly relate your experience with sulfadiazene in the treatment of pneumonia?

DR. B. W. CAREY, PEARL RIVER, N. Y.—Sulfadiazene has been used in 200 cases of pneumonia treated at Detroit under Dr. Cooley. This drug may be used safely if hemorrhagic nephritis is present provided the urinary output is good. Urinary complications must be looked for. Sufficient body fluids must be maintained.

DR. J. A. JONES, SWARTHMORE, PA.—Does blood level of sulfathiazole in meningitis suffice even though spinal fluid level is low?

DR. FINLAND.—Even though spinal level cannot be maintained with sulfathiazole, it is effective in meningitis. Staphylococcus meningitis has been cured with sulfathiazole even with low spinal fluid concentrations.

DR. J. A. V. DAVIES, BOSTON.—In meningitis spinal fluid level is not so important. Blood level in pyelonephritis is also more important than urine level. In staphylococcus infections we still have not found the most desirable remedy. Transfusions are of value.

TWELFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CHICAGO, ILL.—NOV. 4-7, 1942

Report of the Secretary

This year has been a busy one for the Secretary as it has been for everyone else. The change from peace to war has, of course, brought burdens which none of us could have foreseen.

The Academy now has some two hundred of its members in the various services and they are going in more and more every day. However, a survey of the membership of the Academy showed that when divided into age groups, the total under 45 years of age, exclusive of women, was something over five hundred; while those over 45 years of age, together with the women, was pretty close to a thousand. This means that the majority of the members in the Academy are over 45 years of age and it is not likely that many of the men over that age will be called to service. The members know, I think, that we have done away with any collection of dues from those in service and that arrangements have been made for them to obtain THE JOURNAL OF PEDIATRICS at our usual rate of five dollars per year.

Of course, the men in service by no means represent all the various activities in which our members are engaged in the war effort. Many of them are doing yeoman service in their local communities and some are very much involved in national movements; for instance, our Committee on National Defense and our Committee on Nutrition.

We have recently had a request from the American Legion to give them professional advice regarding a program on child health and nutrition. This has not progressed as far as it might have, because the Legion changed its plans after we were well started. From a problem on nutrition, they have changed to one which takes up the whole of child health, both physical and mental, as well as social. We were not prepared for such a program, and it may be necessary to develop a special committee to meet this situation. This program consists of a series of eight sound-slide demonstrations.

Partly as a result of the closer approach of the United States to the Latin American countries, there has developed at this time an effort on the part of the Academy to associate Latin American pediatricians in the Academy with the same amount of preparation as our own members. For that purpose the Secretary was authorized to go to Mexico where he had a delightful reception from the Mexican pediatricians and, as a result, returned with fifteen applications for membership and probably more to come. These applications were on a modified basis in that the Executive Board felt that, under the circumstances, we should not demand an initiation fee from the Latin American pediatricians, and that there should be a reduction to them in the annual fee. The Secretary will make a more detailed report on this at the Business Meeting. In the meantime, it should be said that this effort has been made possible not only through the contact already mentioned but previously to a large extent very successfully by our Committee on Pan-American Scholarships. These scholarships total the number of twenty, and their development is one of the things of which the Academy can be most proud.

The Secretary wishes to call attention to the excellent work which is being done by the Committee on School Health. This Committee is having a very strong influence on activities with respect to the care of children in schools. It is fast becoming a body to which school superintendents and executives appeal for advice on this subject. It is closely coordinated with the American Public Health Association and has done a grand job.

Your attention is called to the attempt to develop a museum and library within the Academy. Anyone who has any ideas or suggestions along this line, I am sure, will receive prompt attention from the Chairman of that Committee, Dr. Edgar E. Martmer.

There have been repeated suggestions by members that we have a "key." This suggestion has been combatted by another group within the Academy. To determine the expression of opinion of the Academy on this matter, a vote was taken last spring, with the result that of 694, 420 were against and 183 for, and 91 had miscellaneous suggestions.

The Secretary is sorry to report the deaths of the following members:

Dr. Harry M. Greenwald, Brooklyn, N. Y.
Dr. George K. Hagaman, St. Paul, Minn.
Dr. Alice K. Higgins, Rockville Center, N. Y.
Dr. W. Myers Hunter, Charlotte, N. C.
Dr. David Levy, Detroit, Mich.
Dr. Merle Pierson, Detroit, Mich.
Dr. Ellen S. Stadtmuller, San Francisco, Calif.
Dr. Kenneth D. Blackfan, Boston, Mass.
Isadore R. Rothstein, Irvington, N. J.
Maurice L. Ripps, Elizabeth, N. J.

Emeritus Fellows

Dr. Maynard Ladd, Boston, Mass.
Dr. Frank Leech, Washington, D. C.
Louise Taylor Jones, Washington, D. C.

Respectfully submitted,
CLIFFORD G. GRULEE
Secretary

Report of Region I

Region I has concerned itself during the past year mainly with the Wartime Child Health responsibilities of the Fellows of the Academy. Never before have our Fellows faced such a heavy burden with rapidly diminishing personnel.

In collaboration with national, state, and local governmental and non-governmental agencies, our Academy represents the chief reservoir of pediatric knowledge, from which must come the Child Health leadership during this war.

Unless every child in America, through the difficult days that lie ahead, has opportunity to get physical fitness for his body, develop mental courage for his mind, and high ethical and spiritual ideals for his soul, the war will have been lost for us, even if the nations led by good ideals and fighting for the perpetuation of human freedoms win the war, and civilization, as we have known it, continues.

The children of today must reconstruct the better world of tomorrow, with more equality, freedom, and fraternity than we succeeded in building into it. They cannot possibly accomplish this unless we see to it that they have sound health in body, mind, and soul, and train them to keep their eyes eternally fixed on the high ethical and spiritual ideals of mankind and not sink into the materialistic philosophies of men and nations alike which have brought this world into its present state.

The evil Nazis have trained their children and youth to worship a brass god named Hitler—the crafty Japanese have trained their children and youth to worship a puny puppet emperor, styled "The Son of Heaven," and to die fanatically for him. The Nazis and the Japanese possess physical fitness and mental courage, but their present ideals are rotten at the core.

We must give our present children and youth physical fitness and mental courage and see that they are also armed with the simple faith and high ideals with which our forefathers established these United States and built the American way of life.

If we are to do our part in winning this war by winning this battle of Child Health as outlined, we must lay aside less essential things in the Academy program and concentrate on those activities which will contribute most directly to better physical fitness, better mental courage, and better and higher ideals in our children. We are proceeding along this line in Region I. Our April Philadelphia meeting, under the guidance of State Chairman Lyon and his able General Chairman Tyson, with the loyal and devoted help of all of the splendid, hard-working Philadelphia Fellows (in addition to an excellent scientific pediatric program and exhibit), was largely devoted to a comprehensive review of the Wartime Child Health Responsibilities of our Fellows and a detailed presentation of the major Wartime Needs of Children.

Our State Chairmen's meeting covered the same ground, with exchange of State Chairmen's experience along these lines, in which national Academy Officers and Children's Bureau officials participated.

To further ascertain the present situation in each of the states and provinces of Region I, a September, 1942, questionnaire as to the main Wartime Child Health Needs was sent out to all state and province chairmen. (The detailed reports of each state and province chairman will be available at the registration desk at Chicago, for examination by interested Fellows.)

The situation as to the following wartime child health important needs in Region I as shown by our reports is as follows:

1.—As to the status of the prevention and control of communicable diseases, showed a good control in virtually all states and provinces.

2.—As to the Academy being officially represented on the state and local defense councils, showed that half of the states and provinces were so represented.

3.—As to cooperative plans of the state or province Academy with the State Bureaus of Child Hygiene as to important wartime health needs of children, such as good medical care, evacuation, and reception plans, showed that in general good medical care for children had not, as yet, been impaired, except in some industrial and military defense areas. A majority of the states and provinces had set up evacuation plans, but only a minority had reception plans.

4.—As to State plans cooperating with health and welfare departments as to setting standards for health supervision and medical care for children of working mothers in day nurseries or day-care centers, showed that this had been accomplished in nearly all states and provinces. Connecticut, in particular, had an excellent program of standards for child care centers, which will be on file with the reports at Chicago.

5.—As to nutrition programs for children in the states, showed universal progress in our states along this line.

6.—As to lack of good medical service for children in military or industrial defense areas, where increased shortage of medical personnel or increased population or other conditions played a part, showed a number of our states, particularly our industrial states, where there was a definite lack of child health medical services in some areas.

7.—As to any other programs contributing to wartime child health needs, such as mental hygiene, school health, etc., showed that our state and province chairmen and Fellowship, without exception, are awake to the importance of these and other wartime child health problems and are carrying on numerous activities contributing to better child health along many lines in their states.

In these difficult days, these reports lead to a considerable degree of pride in the good child health leadership of our State and Province Chairmen in Region I and hearty cooperation by their Fellows. Our thanks are due to them for their steady, continuing contributions to the Academy's ideals.

Oliver Wendell Holmes once said, "Better light a candle than curse the darkness." In the present world-wide darkness, we, Fellows of Region I, intend to keep our eyes firmly fixed on our lighted candle. Working by its light, we will earnestly strive to fashion a transcendent degree of sound health in the bodies, minds, and souls of our children, so that they may build a better world for the future.

Respectfully submitted,
STANLEY NICHOLS
Regional Chairman

Report of Region II

There has been no meeting of Region II since the annual session of the American Academy of Pediatrics last year. This year Region II will meet conjointly with the Southern Medical Association in Richmond, Va., one week following the annual meeting of the American Academy. A most interesting program has been prepared, and I feel sure those who will be able to attend will be well pleased. We are trying an experiment in meeting with the Southern Medical Association because Region II covers such a large territory that the long distance to travel makes it difficult for the pediatricians to attend the two meetings separately. We are further extending our territory by taking in Mexico, Central and South America. The plans for this are about completed.

Respectfully submitted,
HUGH LESLIE MOORE
Regional Chairman

Report of Region III

Region III is pleased to submit for your consideration its report covering the year immediately past.

As of Oct. 15, 1942, the total membership of Region III numbered 426. Fourteen new members were elected to membership at the Board's June meeting. Region III is sorry to record the loss by death of three of its members during the last year: Dr. George K. Hagaman, St. Paul, Minn., Dr. David Levy, Detroit, Mich., and Dr. Merle Pierson, Detroit, Mich. No members have been lost through resignation or for any other reason.

If a service flag were in possession of the Region, it would be privileged to exhibit forty-eight stars on its surface.

Since this report must of necessity be brief, space cannot be afforded for a description of the meeting itself. Suffice it to say that the Cleveland meeting deserves a place well at the top with any of the Region's previous meetings. In the Chairman's opinion, the preliminary publicity for this meeting reached an all-time high and undoubtedly had much to do with the unexpectedly large attendance. The Region owes a debt of thanks to the General Committee on Arrangements, under the Chairmanship of Dr. Edward A. Wishropp of Detroit, and to the Local Committee on Arrangements under the Chairmenship of Drs. Gerstenberger and Toomey for hard tasks superbly performed.

Reports from the various State Chairmen as submitted to the Regional Chairman were particularly gratifying this year. Reports were received from all the states except Colorado, Illinois, and Indiana. While most of the State Chairmen mentioned the difficulties of carrying on child health programs because of the additional in-

dividual loads Academy members have had to assume, nevertheless, the reports invariably reflected accomplishments in the various projects for the betterment of child health in which the Academy is interested. The reports of Michigan, Minnesota, and Missouri may be singled out to illustrate this point. Dr. Frank Van Schoick, Jackson, Mich., who replaced Dr. Cole as State Chairman for Michigan when the latter entered military service, relates the accomplishments of the State Committee on Cooperation with Nonmedical Groups and Societies in his state. Among other things, the Committee prepared pamphlets on contagious diseases for distribution to local health departments; revised recommendations on immunization procedures distributed by the State Health Department; assisted in the preparation of a pamphlet on *School Health Policies* which restated, emphasized, and defined the limitations of a modern school health program; re-emphasized the policy that whenever possible preschool examinations should be done in private physicians' offices; and cooperated with the Detroit Department of Health in setting up standards for operation and management of day nurseries. In addition, the Newborn Nursery Committee set up rules and regulations which have been accepted by the Detroit Obstetric and Gynecology Society, the Detroit Hospital Council Committee, and the Detroit Board of Health.

Dr. Hugh Dwyer, Co-Chairman for Missouri, reports that in Kansas City following a demonstration of tuberculosis case-finding in which some 5,000 persons were examined, the Board of Education issued regulations providing for a physical examination, including an x-ray plate for all teachers and other school personnel. Co-Chairman White of the same state reports that the Committee on Contact Infection in St. Louis has not as yet met with success in having the same regulations adopted in that city.

In Minnesota, Dr. Roger Kennedy reports that among other activities a postgraduate course on the preschool child was presented at the Center for Continuation Study at the University of Minnesota. One of the sessions was devoted to a discussion of the Summer Round-Up and was presided over jointly by the Chairman of the Child Health Committee of the State Medical Association and by the State Chairman of the Summer Round-Up Committee of the Parent-Teacher Association.

Other State Chairmen report the continued activity of local Academy members in connection with governmental programs; e.g., Crippled Children and Maternal and Child Health. Some dissatisfaction was expressed in several states over inability to have rheumatic heart disease in children included in the crippled children's program.

One impression distinctly gained by the Regional Chairman after reviewing the reports of the State Chairmen this year is that the time has arrived when serious attention needs to be given to the problem of coordinating and defining limitations of the various child health programs going on simultaneously and not infrequently more or less independently in the states. The feeling was evident in several of the reports that the "edging-in" of governmental agencies such as local and state health departments, Children's Bureau, and others was being viewed with concern. Whether such concern is warranted can well be a subject for consideration at the Round Table for State Chairmen at the coming Chicago meeting. It is to be hoped that representatives from all groups can be brought together, in the interests of the health of all the children in America.

Respectfully submitted,
LEE FORREST HILL
Regional Chairman

Report of Region IV

We approach the end of our fisrt year of active participation in the war to find the membership of Region IV almost feverishly busy. The demands of private practice have greatly increased; facilities for all manner of technical assistance are curtailed and are rapidly diminishing; we are confronted with new problems and presented with unusual opportunities for service.

In several of the states, there are four members or less, and it has devolved on these few men to carry on not only with the increased demands of practice and with the many new demands engendered by the war, but with the ordinary statewide Academy activities as well. Judging by the reports, these men are carrying out these numerous activities to an astonishing degree.

In the more populous states, a considerable number of the pediatricians have entered Military or Naval Service to encounter different conditions of practice to which they are unaccustomed, but for which they should not be ill suited. Those who remain at home, many of them older practitioners, face the necessity of greatly in-

creased effort that there be no dearth of adequate pediatric care among the civilian population. The coastal states have seen great increases in industrial activity, unprecedented shifts in population, and the consequent creation of new problems for physicians in private practice and for the various agencies having to do with the health and welfare of children in which pediatricians and the Academy are concerned.

It is perhaps unfortunate that the necessity of shortening the Annual Regional Report makes it impossible to include in detail the excellent reports from the various states. Never, during the term of your Chairman, has there been a more prompt response to the requests for reports from State Chairmen or more enthusiastic accounts of the Academy work proceeding in the various states. In every state steps are being taken to meet the problem of childhood care in abnormal population concentrations brought about by Military or Naval encampments or industrial projects. Along the coast the problem of evacuation of both well and sick children is being seriously considered.

The annual meeting of Region IV was not held this year because of the emergency. At the time set for the regional meeting a dinner meeting was held in Los Angeles at the time of the examination of the American Board of Pediatrics. To this meeting all of the members of the Region were invited and about 100 members and guests attended. Lee Forrest Hill and Arthur H. Parmelee were the guest speakers. It is sincerely to be hoped that it will be possible to hold a regional meeting in 1943.

This is my last report as Chairman of Region IV. It is impossible to look back over this period of eight years without some faint sense of regret; so much more might have been accomplished which, for one reason or another, was not done. This eight years has seen a transition of the Academy and the Country from the dismal doldrums of the early 1930's to the hectic activity of the present. The next few years must be critical years for the Academy as for every other American institution, and, like all others, it must depend for survival on its own innate vigor. My association with the entire membership of the Region has been personally very pleasant, and the loyalty and cheerful cooperation of the general membership and of the State Chairmen has caused me to be extremely grateful. I bespeak for the very able Chairman-elect a similar loyalty, which I personally pledge to him.

Respectfully submitted,
EDWARD B. SHAW
Regional Chairman

Standing Committees With State Activities

Report of the Committee on Camps

The activities of the Committee on Camps during the past year have consisted of certain publications appearing in current numbers of *Camping Magazine*, the official organ of the American Camping Association. One of our committee, under the aegis of the Camping Association, submitted a rather detailed form for physical examinations which was circulated among many camp directors and physicians interested in camps. Another more abbreviated form was also published in the *Camping Magazine* and at the same time an article was written which attempted to give the real function of the physical examination, emphasizing its purpose to the camp staff. It was appreciated that no single form for physical examinations would be suitable for all camps and that a uniform acceptance could not be expected. It has been our impression that camp directors now have profitted by these publications. One of the problems yet unsolved in this connection is a follow-up program whereby the camp examination and that made in the school will be correlated.

A further article of a somewhat popular nature on the subject of the evaluation of body weight and height in campers appeared in the *Camping Magazine*. This was written by Dr. Harold C. Stuart of the Harvard Medical School and received very favorable comment. Other articles on subjects such as diet and fatigue will occur later.

In June of this year the United States Children's Bureau called a conference in Washington on young workers in wartime agriculture. The national Chairman of the Academy Camp Committee was asked to attend this conference and assist particularly in formulating standards for the protection and better development of health conditions among young workers in wartime agriculture. It was pointed out that the immediate need for labor from the age group under the draft age did not exist at present, but in the coming years many young people would be undoubtedly called upon to contribute directly to the war effort. This would mean the organization of so-called work camps throughout the country and the allocation of

young people to farms where labor shortage exists. All aspects of the subject were discussed and recommendations formulated for the protection of the young worker. The minimum standards for sanitation, diet, hours of work, recreation, etc. were written into the report. It was recommended that all young workers should have a careful physical examination and the routine immunization procedures be adopted. Although the recommendations of the committee lack power of enforcement, it will undoubtedly be recommended that the state authorities follow the standards formulated by the conference. This meeting of the Children's Bureau concerning young workers may point toward an important development of camping as a direct contribution to our war effort. The need for medical supervision of these young people engaged in agricultural work will increase the responsibility of members of the Academy. Copies of the *Report of Conference on Supervision and Employment Conditions for Young Workers in Wartime Agriculture* may be obtained by writing to the Children's Bureau in Washington.

Respectfully submitted,
WARREN R. SISSON, Chairman
W. L. FUNKHOUSER
ROGER L. J. KENNEDY
VERNON SPICKARD
HENRY E. UTTER

Report of the Committee on Contact Infections

Dr. Roy P. Forbes reports from Denver, Colo., that in spite of the shortage of domestic workers, health examinations have been arranged and are being carried out. In St. Louis, steps are being taken for periodic health examination of the adults of its school personnel. Dr. Hugh Dwyer states that in Kansas City a 35 mm. film x-ray is being used for chest examination of school teachers, boarding home mothers, and domestic employees.

A luncheon meeting was held in Cleveland on May 15, with Dr. Park J. White as Chairman. Drs. Hart Van Riper, Ira Brown Krause, and Horton Casparis addressed the group.

At Philadelphia, during the meeting of Region I, Dr. P. F. Lucchesi presided at the luncheon of the Committee on Contact Infections. Dr. Exner spoke on the health examination of domestic workers which has been conducted for several years by the Department of Health in Newark, N. J. Health cards are required in this city for all who are so employed.

The American Trudeau Society has expressed the desire for a cooperative undertaking with the American Academy of Pediatrics to strengthen the program of education on tuberculosis. It is thought by the Trudeau Society that tuberculin testing of children and adult members of households by pediatricians will result in earlier diagnosis and add to the interest and knowledge in these families concerning the spread of this disease. It is recommended that the follow-up of adult members of the family should be by physicians especially trained in tuberculosis.

To bring about cooperation between these societies the Committee recommends the following program to the members of the Academy:

Prevention of Tuberculosis in Children

1. Every child under pediatric care should be tuberculin tested annually as long as the reaction remains negative.
2. In all families with children, the adult household members and employees should be tuberculin tested. This may be done by the pediatrician at the time the children are tested or at another time by some other physician.
3. A positive reaction should be followed in all instances by a lung x-ray. If preferred, the x-ray may be obtained without a preliminary tuberculin test.
4. When a child is found to have a positive tuberculin reaction, it is imperative to secure lung x-rays of all tuberculin-positive adults with whom the child is in close association.
5. All adults should secure advice and any necessary follow-up in regard to tuberculin reactions, x-ray, and other examinations from physicians with special experience in this disease.
6. Open cases of tuberculosis should be segregated or removed from contact with children until they no longer disseminate tubercle bacilli.

It is important to emphasize at this time the need for prevention of contact infection in children of war workers who are being cared for in groups. Adults who have charge of these children should be proved free from transmissible disease.

Respectfully submitted,

FAIRFAX HALL, Chairman
GAYLORD W. GRAVES
REGINALD A. HIGGONS
CHESTER A. STEWART
PARK J. WHITE

Report of the Committee on Cooperation With Nonmedical Groups

The contacts made by this Committee with educational and health groups in recent years were renewed during the past year. The film, "When Bobby Goes to School," continued to serve a useful purpose in stimulating better health examinations. By action of the Executive Board, the showing of the film for public educational showings was made available to State Boards of Health. Mr. Rose of Mead Johnson & Co. stated at the Regional Meeting in Cleveland that approximately one and one-half million lay people had seen the film and that it had been presented to over four hundred medical societies. The brochure prepared for physicians entitled *Health Appraisal of the School-Age Child* has been distributed to every member of the Academy. Reports from various sections of the country indicate that the booklet filled a real need. Several requests have come from pediatric teachers to supply sufficient copies to distribute to students. The Committee feels that this material can be used effectively in many places that thus far have not applied for it.

Again our Committee cooperated with the National Congress of Parents and Teachers. Fortunately Dr. Lillian R. Smith, a member of this Committee, is also Chairman of the Advisory Committee on Health and Summer Round-up of the P.T.A. At the annual meeting of this advisory group, Dr. Joseph A. Johnston officially represented the Academy. In addition to the country-wide effort to offer health examinations to preschool children, especial appeals were made to encourage vaccination against diphtheria and smallpox. This was in support of President Roosevelt's proclamation for Child Health Day. It was pointed out that nutrition information was decidedly inadequate in many schools and particularly in high schools. The Academy representatives informed this Committee of the need of a teaching film on nutrition. Such a film is now being prepared but is being supervised by the Committee on Nutrition. Preliminary plans are under way for a possible film designed to aid in the health education of adolescent children, but the completion of this film will undoubtedly be delayed during the war emergency.

The new undertaking of the Committee, spurred by the war effort, was the preparation of an outline on standards for the medical supervision of day nurseries particularly for the children of mothers engaged in war industries. Copies of the manual were sent to each State Chairman with the request that local groups interested in the organization of such schools be contacted. In a number of states, members of the Academy have been instrumental in directing the health supervision of these day nursery schools. Undoubtedly during the next year the needs of the emergency nursery schools will increase demanding greater assistance from pediatricians. This year at the annual meeting of the National Association for Nursery Education, our Committee was represented by Dr. William L. Bradford, Chairman of the New York State Committee. This association is concerning itself with standardizing nursery schools throughout the country. At the annual meeting of the National Association the Academy was requested to prepare a statement on the medical aspects of nursery schools and to prepare an examination blank for the National Association for Nursery Schools.

The personnel of the state committees has been disrupted in a number of states due to departure of the chairman or members of the committee into the military service. An attempt has been made to contact the state chairmen through communications on committee affairs and through committee meetings at two regional meetings. At the meetings in Philadelphia and in Cleveland, the duties of the committee were discussed by a good representation of state chairmen. The opinion was generally expressed that our principal task was to aid any agency engaged in the war effort where the welfare of children is at stake. This Committee with the aid of the state groups will endeavor to meet any emergency duties that may arise during the next year pertaining to war effort and civilian defense.

Respectfully submitted,

ALBERT D. KAISER, Chairman
DENNIS H. KELLY, Secretary
JAMES W. BRUCE
GEORGE L. DRENNAN
MARVIN ISRAEL
JOSEPH I. LINDE
MARGARET NICHOLSON
JAMES C. OVERALL
LILLIAN R. SMITH

Report of the Committee on School Health

Medical Standards for Physicians in the Schools

In 1937 the Committee on School Health of the American Academy of Pediatrics proposed five principles to guide in the development of medical services for public schools. Last year the Committee re-emphasized the second principle which was concerned with medical standards and the maintenance of quality of service. We quoted from one of the principles of the American Medical Association: "The responsibility for the character of Medical Service must be borne by the medical profession," and declared, "The advice which is given to parents, pupils, or school staff should meet the best medical standards."

While the soundness of these principles has not been questioned, a neglect of medical standards has been almost characteristic of school service until very recently, and, still, too many places allow the responsibility for the character of medical service to be borne by lay administrators. Organization plans generally provide no way of being sure that the school administrator's decisions will be made with the benefit of a full understanding of medical problems. It is not surprising then that medical standards and quality of service have been neglected so frequently in school health services. In fact, there is such a large proportion of school systems which select their medical personnel and determine the conditions of their employment without real medical leadership that it should be obvious that this phase of public health has not had the kind of medical guidance that it deserves.

It is, of course, recognized that the administration of a school or school system should be directed by an educational authority, but if policies and procedures concerned with obtaining medical care and preventive service for children are to be developed with an understanding of medical needs, then medical leadership is also essential. If the schools are to make a more effective use of their strategic position to educate parents and children to use curative and preventive medical services intelligently, then the great professions of education and medicine must work together in a common cause. Some plan of administration is necessary for educational matters to be guided by educators and for medical policies to be determined by physicians. There must be a plan that avoids decisions made upon administrative convenience only rather than upon professional principles.

Organization Plans.—As the physician in the schools may receive his direction from the health department, the education department, or from a combination of the two departments, we should consider how each type of organization may be planned to conform to our medical principles:

1. The administrator of a school health service under a Health Department should provide for a medical administrator to give direction and leadership in interpreting medical standards in order to obtain the best medical personnel and conditions of employment for the benefit of the public. With civil service or other plans for a merit system, the qualifications of personnel must be decided according to a sound interpretation of needs. A medical executive to study the needs of the schools and the community and to coordinate the school health program with all the public health resources of the community is an essential for community planning. This executive might be either the health officer or his assistant, according to the size of the community and the organization. Either through the Board of Health or through a special medical advisory committee the executive should have the support and advice of a real medical leadership. From the education department he should also have such an organization plan as will provide at all times for ready consultation and leadership of the educational staff.

2. If the administration is under the education department, there is often a problem of obtaining a medical executive for the smaller school systems unless a full-time medical executive can be arranged to serve several school districts, or for the medium-sized school systems, unless the executive can be combined with the medical

staff part of the service on a full-time basis. In either case a medical advisory board is needed to safeguard professional qualifications and conditions of employment for the medical staff.

The plan of a board for determining essential broad policies is an accepted and well-tried plan to safeguard the public welfare by providing advice, support, and control of the executive. The board would insure that disinterestedness in interpretation of all medical matters which is essential for meeting medical needs. It is essential for consideration of problems involving quality of service because of the necessity of medical interpretation to the lay superintendent and his board who have the final authority on the budget. The demand for economy and the tendency for quantity to replace quality of service raises serious questions that should be evaluated by a medical board that is not dependent upon the board of education for their personal employment and security.

3. When the school health service is administered under joint control of the health and education departments, the need for a medical executive can usually be supplied through the health department's contribution, or by a special medical administrator responsible to a joint board. The joint board from both departments should direct or advise the medical staff.

While lay administrators may in some places select well-qualified physicians and consistently accept their advice without the help of a medical advisory board, the control of such essential and highly specialized personnel as physicians should not be left to the chance possibility that a lay administrator or board will know how to obtain qualified physicians. Professional standards of qualification should be used as a guide by a medical administrator or medical board, but no formula to be applied by laymen should be accepted as a substitute for medical leadership in the selection and control of medical personnel. Sound public service demands that the public always have the benefit of the recognized channels of organized medicine for determining medical standards. If these standards are to be applied for the selection of medical personnel and for determining the conditions of employment for physicians, then an organization plan must provide the means for interpreting how the standards may best meet the needs of an individual situation.

Professional Qualifications.—There is, therefore, need for two kinds of professional standards for medical personnel:

1. Medical administrator
2. Staff physician

The medical administrator should meet, in addition to basic pediatric training, standards of training and experience in public health administration and education; and the staff physician should meet qualifications in clinical and preventive pediatrics.

While full-time medical personnel is recommended for administrative positions, the requirement of full time for staff positions is likely to discriminate against the more competent, ambitious, and well-qualified clinicians because the more competent physicians are not likely to be willing to give up the rewards available to them through private practice. Until the pay for staff positions can be made very much more inviting, the most competent physicians will be available for staff positions only on a part-time basis. Unless we are to sacrifice quality of medical judgment that is so much needed to advise parents, teachers, and nurses, we should, therefore, propose a plan for selection of the best qualified physicians available in the community for staff positions; and it should be recognized that the part-time physician engaged in private practice is likely to bring to the schools more clinical qualifications than the full-time physician who receives a salary below the executive level. The decision as to selection for such staff positions is distinctly a medical problem, and the standards for the positions should be determined by a medical board or the Board of Health. The pay should always be sufficient to attract the best qualified young physicians of the community who are practicing pediatrics.

In so far as qualified physicians are available, preference should be given to those physicians who meet the following qualifications in the order named:

1. Diplomate of the American Board of Pediatrics
2. Fellow of the American Academy of Pediatrics or qualifications meeting Academy requirements
3. Alumnus of hospital registered by A. M. A. and with residency or fellowship in pediatrics
4. Alumnus of hospital registered by A. M. A. which includes service of one year in pediatrics where there is an approved residency or fellowship in pediatrics (Communicable Diseases included in pediatrics)
5. Alumnus of hospital registered by A. M. A. (one-and-one-half-year internship) and an appointment in pediatrics to a registered hospital (including O. P. D. or hospital appointment)
6. Part-time specialty in pediatrics with pediatric appointment in registered hospital

Standing Committees

Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases

Revision of the pamphlet has just been accomplished.

Respectfully submitted,

JOHN A. TOOMEY, Chairman
BENJAMIN W. CAREY
E. J. HUENEKENS
CHARLES F. MCKHANN
BELA SCHICK
HULDAH E. THELANDER

Committee on Legislation

No matters of general legislation have come before the Committee on Legislation since its last report.

The Committee has been instrumental in drawing up certain proposed amendments to the By-Laws to be presented at the Annual Meeting of the Academy in November, which will be brought to the attention of the membership at that time.

Respectfully submitted,

JOSEPH S. WALL, Chairman
JAY I. DURAND
HARVEY F. GARRISON
PHILIP VAN INGEN
ALFRED A. WALKER

Report of the Committee on Mental Health

The production of the motion picture, "Emotional Growth During Infancy," which was made possible by a grant from the Pet Milk Company, has been temporarily held up because of the war. The scenario is nearly completed and permission for the production has been obtained from the Government. It will be completed as soon as the producer has disposed of films urgently needed by the Government.

Since people naturally turn to children's programs during war and because the mental health of children is of vital importance, the Committee feels that this subject should receive a more important place on the national and local programs.

Respectfully submitted,

BERT I. BEVERLY, Chairman
C. ANDERSON ALDRICH
FREDERICK H. ALLEN
HORTON CASPARIS
BRONSON CROTHERS
GEORGE J. MOHR
ARTHUR H. PARMELEE
VICTOR E. STORK

Report of the Committee on Nursing Education

During the past year this Committee has made some progress advising with a Subcommittee for the Study of Advanced Courses in Pediatric Nursing of the National League of Nursing Education. We have assisted in outlining the medical content of the pediatric courses. Such experimental courses are being used in the School of Nursing Education in The Children's Hospital of Cincinnati and are proving very satisfactory.

This Committee also feels that the medical content of courses taught nurses in their undergraduate pediatric training should be given a good deal of thought and

an attempt made to set up a guide as to the medical content. The Academy Committee is now considering this problem with one of the committees of the National League of Nursing Education.

The shortage of nurses at the present time, due to the national emergency, does not favor efforts on our part to try to establish minimum educational requirements in each state for entrance into Grade A nurses' training schools. However, the justification for such minimum requirements is still recognized as paramount by this Committee, and in the future possibly something definite may be accomplished.

Respectfully submitted,
MERLIN L. COOPER, Chairman
STANLEY GIBSON
WILLIAM P. LUCAS
WILLIAM WESTON
CHARLES A. WEYMULLER

Report of the Committee on Pan-American Scholarships

The year just passed has been a most momentous one in Pan-American relationships. December 7 has emphasized the importance of unity in Pan-America. Your committee feels that in spite of the state of war, it has great progress to report. As you may recall, our three Pan-American scholars, Dr. Madero of Mexico, Dr. Meneghello of Chile, and Dr. Cardelle of Cuba, were present at the Boston meeting and brought a message of good will to the Academy from their native countries. Dr. Madero and Dr. Cardelle have completed the time of their scholarships and have returned to their homes. Dr. Meneghello is still working at Johns Hopkins University in a six months' extension of his scholarship.

During the year three new scholars have been appointed. Dr. Leopold Benedetti of Panama holds the Procter scholarship at the University of Cincinnati. Dr. Hernan Hedderich of Venezuela holds the Quaker Oats Company scholarship and is working at the University of Chicago, and Dr. Arnulfo Valencia of Colombia, holding one of the new W. K. Kellogg Foundation scholarships, will work at Harvard University. As soon as all the formalities of our arrangements with the Ecuadorian Committee can be gone through with, we hope to appoint the scholar that it has recommended. The appointment of new scholars from Mexico and Cuba will be made in the very near future.

The contacts made at the Pan-American Child Congress in Washington last May have been very helpful in giving publicity to our scholarships, and they gave us an opportunity to discuss the problem of the selection of scholars with men from the various countries who will be likely leaders in establishing cooperating committees of the national pediatric societies.

Your Committee has the privilege to announce at this time the establishment of thirteen new Pan-American scholarships through the generosity of the W. K. Kellogg Foundation of Battle Creek, Mich. To its president, Dr. Darling, we are greatly indebted not only for making these scholarships available, but also for the helpful hints he has given us in our work. With these additional scholarships the Academy is now in a position to broaden the scope of its work and make scholarships available to all the republics south of us. With the scholarships already given by the Mayo, Procter, and Wisconsin Alumni Foundations, and by Abbott Laboratories, M & R Dietetic Laboratories, Mead Johnson & Company, and Quaker Oats Company, there are now twenty scholarships available.

From my presidential address in 1939 I quote: "I should like to suggest that the Academy interest itself in procuring scholarships in American pediatric centers for promising young pediatricians of Central and South America." The scholarships are now available and the much greater task of administration is now before us. This, we believe, cannot be carried out by a Committee. Your Committee therefore suggests to the Executive Board that it be continued in an advisory capacity and that as soon as possible the administrative work be carried on by an executive officer attached to the central office of the Academy.

The following new committee has been appointed:

In Colombia:

Dr. Calixto Torres-Umana, President
Dr. Eustacio de Mendoza, Secretary
Dr. Jorge Camacho Gamba
Dr. Hector Pedraza Mendoza

Respectfully submitted,
HENRY F. HELMHOLZ, Chairman
SAMUEL Z. LEVINE
FREDERIC W. SCHLUTZ
FRANCIS SCOTT SMYTH

Special Committees

Report of the Committee on a Library and Museum of Pediatrics

The Committee on a Library and Museum of Pediatrics of the American Academy of Pediatrics has made a preliminary survey of the subject of a National Pediatric Library and Museum and wishes to submit the following report:

There is no provision at the present time for the preservation of objects of interest in the field of pediatrics except that a few individuals and commercial firms have collected such objects on their own initiative.

Objects of pediatric interest are being placed in general collections rather than in specialized collections.

Objects of pediatric interest are being lost forever as they are discarded by persons who fail to recognize their importance and historic value.

Many of the pioneers in pediatrics in this country are reaching an age which makes it essential that some provision be made for them to place their material in a place of safety if it is to be preserved.

One of the largest libraries of Pediatric Literature in America is available as a start toward a Pediatric Library and Museum of National scope.

In view of these facts, your Committee recommends that the American Academy of Pediatrics invite the American Pediatric Society and the Pediatric Section of the American Medical Association to join with it to carry out the following program:

1. To make provision for the acquisition through gift and other means of such material as is available.
2. To contact all physicans with a view of obtaining by gift and other means all material of historic value whenever available.
3. To store such material in a safe place for the immediate future.
4. To determine the best manner in which such material may be preserved for the future and be made available to those interested in Pediatrics.

Respectfully submitted,

EDGAR E. MARTMER, Chairman
ERNEST CAULFIELD
ALBERT D. KAISER
HUGH MCCULLOCH

Report of the Committee on Mothers' Milk Bureaus

The work of this Committee has been largely one of formulating standards for the most efficient and hygienic operation of Mothers' Milk Bureaus, with a view toward the use of such standards for the legal licensing of these agencies should such control be deemed wise. Dr. Laws in particular, as well as other members of the Committee, has been drawing up such standards, and it is hoped that final action upon them may be possible at the annual meeting in November, or soon thereafter.

In these times of increased birth rate, rising wages, and the employment of many young women in industry, there is a strong tendency for the abandonment of breast feeding. This results not only in a scarcity of women able to sell their milk through directories, but also in an increase in the demand made upon such agencies for breast milk to feed sick infants whose mothers are unable to nurse them. It is the hope of your Committee members that the American Academy of Pediatrics will take every opportunity to advocate the breast feeding of infants.

Respectfully submitted,

CLEMENT A. SMITH, Chairman
CARL H. LAWS, Secretary
JULIUS HESS
E. EARL MOODY
WILLIAM J. ORR
ARTHUR G. QUINN

Report of the Committee on National Defense

The Committee on National Defense held an important luncheon meeting at the time of the annual convention of the American Academy of Pediatrics in Boston in October, 1941, and arranged an evening program on the subject of National Defense for that evening, at which the Committee Chairman read a report, and Drs. Harold Stuart, Martha Eliot, and Thomas Parran read important papers which were subsequently published in THE JOURNAL OF PEDIATRICS for December, 1941. During the year since then, the various subcommittees of the General Committee have continued to function.

In federal activities, the Committee is well represented in Washington by Drs. Wall, Bain, Bier, Sebrell, and Donnally. Dr. Joseph S. Wall has been invited by Miss Katharine Lenroot to represent the Committee on the Children's Bureau's Com-

mission on Children in Wartime, and he has attended one conference of that Commission. There certainly are many possible ramifications in the protection of the interests of children from the deleterious effects of the war.

Dr. Joseph Stokes, Jr., in Philadelphia, was in close contact with the Office of the Surgeon General of the United States Army about the use of pediatricians in the Army, until his Subcommittee's activities were largely replaced by the Office of Procurement and Assignment. It is felt that the need for doctors in the Army is so great that efforts to see that pediatricians are used only in those activities for which they have special abilities, such as contagious diseases, cannot very well be stressed.

Groups of refugee children have come in to New York on two or three occasions during the past twelve months, and medical care was provided by groups of pediatricians obtained by the Subcommittee headed by Dr. Rustin McIntosh. There have continued to be instances of individual consultation and care for various of these refugee children. For the next year, the immediate prospects are that many more refugee children will be brought in by the United States Committee for the Care of European Children, and there will be much further need for medical supervision, which, in view of the shortage of doctors remaining in civil life, will be difficult to provide. This activity is already consuming much of the Committee Chairman's time and promises before long to involve many pediatricians, both Fellows of the Academy and others.

As to the use of pediatricians in plans for evacuations, the actual plans, should evacuations be necessary, must be worked out by national, state, and local organizations on which pediatricians should be represented, but the prime responsibility is not with the pediatricians. However, there is considerable opinion that mass evacuations of children are not desirable.

The Committee would welcome suggestions concerning enlarging the scope and enriching the nature of its activities. The present members are:

Katherine Bain, Washington
Robert A. Bier, Washington
Allan M. Butler, Boston
H. H. Donnally, Washington
Clifford G. Grulee, Evanston
Carl H. Laws, Brooklyn
Edgar E. Martmer, Detroit
Rustin McIntosh, New York
Edward C. Mitchell, Memphis
Edwards A. Park, Baltimore
William H. Sebrell, Washington
Richard M. Smith, Boston
Lendon Snedeker, Boston
Philip M. Stimson, New York
Joseph Stokes, Jr., Philadelphia
Borden S. Veeder, St. Louis
Joseph S. Wall, Washington

Respectfully submitted,

PHILIP M. STIMSON, Chairman

Report of the American Board of Pediatrics

The members of the American Board of Pediatrics appointed by the American Academy of Pediatrics submit the following report of the work of this Board from October 1, 1941, to October 1, 1942.

As in the past two years, we are holding both written and oral examinations for all eligible candidates. Four examinations have been held since the last report, as follows: Boston, Oct. 7 and 8, 1941; Philadelphia, March 30 and 31, 1942; Los Angeles, April 21 and 22, 1942; and Cleveland, May 12 and 13, 1942.

In these four examinations held during this period, 273 applicants were examined, of which 21.6 per cent were either failed or conditioned, while the remainder (78.4 per cent) passed the examinations and were certified. The mortality this year was slightly higher than the previous year.

The new Directory of Medical Specialists published by the Advisory Board for Medical Specialties is off the press, and for the most part seems to be in good order. As in the past, this Board has been cooperating in the publishing of this Directory.

We have also been called upon to furnish the Bureau of Procurement and Assignment of the War Department with various lists and information. It is the feeling of all members of this Board that we should continue to assist the Surgeon General's Office in any way possible during the present emergency.

At the meeting of the Advisory Board for Medical Specialties in Chicago in February, 1942, the Bureau of Procurement and Assignment, represented by Major Sam Seeley, definitely signified its intentions of cooperating with the specialty boards and giving the men who have been certified as much consideration as possible. To date, the officials of both the Army and the Navy have been more than cooperative, and I am sure they will continue to be.

To date, we have not changed our ruling with regard to the examination of applicants being called into service and no action, if any, will be taken before the annual meeting of the Board on Nov. 1, 1942.

Due to the fact that the reports of our auditors over the past three years have shown that it is costing considerably more to examine each applicant than the former fee of $30.00 maintained before the fee was raised to $50.00 on May 1, 1942, we feel fairly certain that this raise will take care of the situation for sometime to come. The Board wishes to call your attention to the fact that the fee of the pediatric board has always been much lower than that of any of the other boards and still is one of the lowest.

Dr. Borden S. Veeder, President of the Board from its founding up until the Fall of 1941, retired from the Board and Dr. Hugh McCulloch of St. Louis was elected for a six-year term in his place by the Academy, as you know. Dr. Philip Van Ingen, elected by the American Pediatric Society, resigned last Spring and Dr. Donovan J. McCune of New York City was elected to fill his unexpired term of four years. Dr. E. B. Shaw of San Francisco was re-elected by the Section on Pediatrics of the American Medical Association for a term of six years at their meeting in June, 1942. At the annual meeting of the Board in Boston last October, Dr. Horton Casparis of Nashville was elected President, Dr. E. B. Shaw of San Francisco, Vice-President, and Dr. C. A. Aldrich of Chicago, Secretary-Treasurer. The office of the Secretary is now at the Children's Memorial Hospital, 707 W. Fullerton Ave., Chicago, Ill.

At the Boston meeting of the Board, the term of office for Board members was discussed, and it was the feeling of all members that this term should be modified. It was finally decided that a term of six years instead of nine years would be more in order. This would put two men off the Board every other year and one man every other year. The Board hopes this change of policy will meet with the approval of the Section.

Applications continue to pour in from all sections of the country. This is partly due to the fact that the younger men wish to get their examinations out of the way before going into military service and partly because Group I (ten years in pediatrics) is to be abolished on July 1, 1943.

During the next six months we are holding four oral examinations as follows: Chicago, Nov. 1, 2, and 3, 1942; New York City, Dec. 4, 5, and 6, 1942; St. Louis, March 27 and 28, 1943; and New York City, April 24 and 25, 1943. The applicants for the Fall examinations took their written examination on September 18. Applicants for the Spring will take their written examination on February 12, 1943.

Respectfully submitted,

HUGH MCCULLOCH
HAROLD STUART
ALFRED A. WALKER

News and Notes

Dr. Horton R. Casparis of Nashville died suddenly of heart disease in Richmond, Virginia, on November 11th while attending a meeting of the Southern Medical Association of which he was a member of the board of trustees.

Dr. Casparis was Professor of Pediatrics at Vanderbilt University and was widely known in his community, the state of Tennessee and the South, and nationally for his broad field of work in pediatrics and public health. He had been particularly interested in tuberculosis and mental hygiene. The esteem in which he was held may be indicated by the recognition given him by many societies and organizations. He was a Fellow of the American Academy of Pediatrics and the American Pediatric Society. He was president of the American Board of Pediatrics and had just been re-elected at the annual meeting of that board in Chicago the week preceding his visit to Richmond. He was on the Advisory Editorial Board of the American Journal of Diseases of Children.

He was chairman of the Maternal Section of the Medical Advisory Committee of the Children's Bureau, and his advice was constantly sought officially and non-officially by the Children's Bureau and other government agencies. He was also a member of the board of trustees of the National Tuberculosis Association and the American Public Health Association. He gave freely of himself to all these and many other organizations. His unfortunate and untimely death will be a great loss to all these and to his personal friends everywhere.

It is with deep regret that the Editors of the JOURNAL announce the death on November 9, 1942, of Dr. Charles Virgil Mosby, founder and Chairman of the Board of The C. V. Mosby Company, of St. Louis, publishers of THE JOURNAL OF PEDIATRICS. Dr. Mosby was a most unusual personality with a courage and a vision that all who knew him recognized and admired. In addition to building up a noteworthy list of medical texts which have had wide recognition and acceptance, the Mosby Company, under Dr. Mosby's guidance, developed a strong group of independent journals in the special fields of medicine. For many years Dr. Mosby had wanted to publish a journal in the field of pediatrics and insisted there was a place and need for another journal, a viewpoint which he held almost alone. In 1931 when the American Academy of Pediatrics decided to have its own controlled pediatric journal, the matter was discussed with a number of publishers. With the exception of Dr. Mosby, every one said a new journal at that time could not be established and would have nothing to do with the idea. Dr. Mosby, however, was willing to undertake its publication and assume entire financial responsibility and to turn over the entire editorial direction and control to the Academy. The Editors have always worked in complete harmony with Dr. Mosby and his company, and he has accepted every decision of the Editorial Board. He took great pride in THE JOURNAL OF PEDIATRICS, its medical standing and position, and cooperated with and aided the Editors in every possible way. Only those familiar with the founding of the JOURNAL have known of the indebtedness of the Academy to Dr. Mosby for his courage and vision and faith in the pediatricians as a group. To those who came to know him closely, his death is a very personal loss.

B. S. V.
H. McC.

A Medical Externship in Clinical Child Development

An externship in The School of Medicine, Yale University, providing clinical training in developmental diagnosis, will be open in 1943 to a qualified graduate (man or woman) of a Class A medical school. The appointment will be for a one-year period, subject to individual arrangement, and carries a stipend of $750.00.

It is assumed that the candidate has a primary interest in clinical pediatrics, neurology, or child psychiatry. The externship is designed to furnish a well-rounded training in methods and principles of developmental diagnosis with special reference to infant behavior. Opportunity for related clinical research can be arranged.

Inquiries and applications may be addressed to: Dr. Arnold Gesell, Director, The Clinic of Child Development, The School of Medicine, Yale University, New Haven, Conn.

The Yale Clinic of Child Development conducts an Infant Outpatient Service with a diversified intake, including normal infants referred for adoption and foster home placement, infants with developmental defects and deviations, and infants presenting behavior disorders. A Diagnostic and Advisory Service for preschool children, conducted in connection with the Guidance Nursery of the Clinic, is concerned with personality development, emotional problems, and child and parent guidance. Each service is in charge of a pediatrician.

The extern has liberal opportunities for observation, conference, and actual practice, and is given increasing responsibility as diagnostic skill develops. Follow-up work is stressed.

The application should include (a) an informal but concrete statement of the applicant's underlying aim and professional interest, (b) a summary of academic record and postgraduate experience, (c) two or three letters from medical sponsors. Further credentials and recommendations are not expected on the initial application. Most weight will be placed on letters from sponsors who can speak concretely and confidently concerning clinical aptitude and adaptability. An interview will be required before final appointment.

Comments

Greetings

THE JOURNAL OF PEDIATRICS brings its felicitations and best wishes to Dr. Isaac A. Abt, the first President of the American Academy of Pediatrics, on the occasion of his seventy-fifth birthday Dec. 18, 1942.

Twelfth Annual Meeting

The twelfth annual meeting in Chicago in November was an important milestone in the life of the Academy. The total attendance of 857, including 445 members, was surprising in view of approximately 200 members being in active service and so many others having to remain at home as a result of added responsibilities at the present time.

Several actions of unusual importance were taken. It was decided that the Annual and Regional meetings shall be omitted in 1943. The reasons for this are so obvious they do not need discussion. The second important action was a change in the by-laws, creating a fifth Region to be called "Latin-American Countries," and further supplementing changes which permit the taking in of our pediatric colleagues from these countries on a full-membership basis. Thus the American Academy of Pediatrics becomes truly "American." Each country for the present will be organized similar to the states and provinces with a Chairman. Small nucleus groups are being organized in several of the countries that will nominate candidates for membership who must fulfill the essential requirements for membership as stated in the by-laws with the exception of certification by the American Board of Pediatrics. As a result of the visit of the Secretary to Mexico last summer, a group of fifteen was organized who were elected to membership at the Chicago meeting. Thirteen Latin American Academy Scholarships have been given by the Kellogg Foundation which makes twenty now available. In a few years, as the result of these scholarships, we should have a large group of Fellows in the Latin American countries with whom we will have a close personal friendship.

One of the most important sessions of the meeting was a Round Table Discussion on the Activities of State Chairmen under the leadership of Dr. Lee Forrest Hill, Regional Chairman of Region III. The meeting was attended by representatives from 38 states and provinces, the Executive Board, the Chairmen of Committees having state functions, and representatives of the Children's Bureau. Many matters were discussed and the meeting could well have been extended to an entire day. In the Executive Committee report recommending that the Annual and Regional meetings be omitted in 1943, it was suggested that local state meetings be encouraged for the purpose of maintaining and continuing child health efforts in wartime and that meetings of State Chairmen shall be called if at any time deemed advisable by the Executive Board or by Regional Chairmen. In remarks made at the State Chairmen's Luncheon, the incoming president stated that he considered that the matter of the functioning of the Academy during the next year was chiefly in the hands of the State Chairmen, and they now had a responsibility such as never before.

On Wednesday evening, in addition to the announced speaker, Dr. Frank G. Boudreau, Executive Director to the Milbank Fund, who spoke on "Medicine in a

Postwar World,'' the Academy was fortunate in having an additional guest, Sir John Boyd Orr, F.R.S., Director of the Rowett Institute of Aberdeen, Scotland, who made a most interesting talk on ''Food and Nutrition in War and Peace.''

The first E. Mead Johnson Award was given to Dr. David Bodian, Baltimore, Md., and Dr. Howard A. Howe, Baltimore, Md., who presented ''A Note on the Penetration of Poliomyelitis Virus From the Gastrointestinal Tract of the Chimpanzee,'' and the second award to Dr. Harold E. Harrison and Dr. Helen Harrison, Chicago, on ''The Renal Excretion of Phosphate in Relation to the Pathogenesis of Rickets and the Mode of Action of Vitamin D.''

The customary floor show and dance following the Annual Dinner was replaced this year by a speaker, Dr. Gerhard Schacher, who spoke on the topic, ''Why Hitler Will Not Win This War.''

The Round Table and Panel Discussions were unusually good, and great credit must be given to the Program Committee for the splendid leaders and others participating in the various discussions.

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